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# BMJ Paediatrics Open

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

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3 **1 Development and validation of a risk prediction model for medication administration**  
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5 **2 errors in neonates: a study protocol**  
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3 **51 ABSTRACT**  
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6 **52**

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8 **53 Introduction**  
9

10 Medication administration errors (MAEs) are the most commonly occurring type of medication  
11 errors (MEs) and they are found to be more common amongst neonates as compared to adults.  
12 They also result in severe patient harm and significant economic burden to the healthcare  
13 system. Targeting and prioritizing neonates at high risk of MAEs is crucial in reducing MAEs.  
14 To the best of our knowledge, a predictive risk score identifying neonates at risk of MAEs is  
15 not yet available. Therefore, this study aims to develop and validate the risk prediction model  
16 to identify neonates at risk of MAEs.  
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31 **62 Methods and analysis**  
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33 This is a multicentre, nationwide, prospective direct observational study in which a minimum  
34 of 1,097 preparation and administration of medications are directly observed. Data such as  
35 patient characteristics, drug preparation and administration related data, and other procedures  
36 will be recorded. After each round of observation, the observer will compare his/her  
37 observations with the prescriber's medication order, hospital policies and manufacturer's  
38 recommendations to determine whether MAE has occurred. To ensure reliability, error  
39 identification will be independently performed by two raters after the completion of data  
40 collection for all study sites. Any disagreements will be discussed with the research team for  
41 consensus. To reduce overfitting and improve the quality of risk predictions, we have pre-  
42 specified a priori our analytical plan such as prespecifying the candidate predictor variables,  
43 handling of missing data and validation of the developed model. The model's performance will  
44 also be assessed. Finally, various modes of presentation formats such as a simplified scoring  
45 tool or web-based electronic risk calculators will be considered.  
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**77 Ethics and dissemination**

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

82

**83 What is already known on this topic**

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

91

**92 What this study adds**

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

96

**97 How this study might affect research, practice, or policy**

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

## 101 INTRODUCTION

102

103 Medication errors (MEs) may arise throughout the medication use process which consists of  
104 prescribing, transcribing, dispensing, administration, and monitoring [1]. Medication  
105 administration errors (MAEs) were found to be the most commonly occurring error as  
106 compared to prescribing and dispensing, amounting to more than 50% of all MEs [2, 3]. MAEs  
107 were not only associated with the highest number of incidents resulting in death and severe  
108 harm as compared to the other stages of the medication use process, but they also lead to  
109 significant economic burden from the utilization of healthcare services [4, 5]. It is estimated  
110 that approximately 4000 patients may be harmed from a total of 6 million medication doses  
111 administered among hospitalized patients and this is expected to consume between USD25 and  
112 35 million annually [6]. A systematic review of all types of MEs reported that the prevalence  
113 of MAEs amongst neonates is found to range between 31% and 63% as compared to adults  
114 which ranged between 14.6% and 41% [7].

115

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



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3 125 to direct observation and chart review [15, 16]. Apart from that, the use of incident reports  
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5 126 meant that major risk factors such as nurses' workload could not be analysed [14].  
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10 128 Given that the prevalence of MAEs amongst neonates have been reported to be as high as  
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12 129 94.9% [17], a validated model incorporating an extensive list of potential risk factors associated  
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14 130 with MAEs should assist all healthcare professionals involved in the medication use process to  
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16 131 identify at-risk neonates in a clinical setting. To the best of our knowledge, a predictive risk  
17  
18 132 score to identify neonates at risk of MAEs specifically is not yet available. Therefore, this study  
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20 133 aims to develop and internally validate the multivariable prediction model for the identification  
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22 134 of MAEs amongst neonates using a prospective direct observational study design, and to then  
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24 135 externally validate the model using a different data set of neonates. The usability of the risk  
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26 136 prediction model in terms of risk stratification will also be evaluated.  
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## 33 138 **METHODS**

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37 140 This study will be conducted in accordance to recommendations by experts for the development  
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39 141 and validation of the model [18, 19]. The reporting of this study protocol will be guided by the  
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41 142 checklist for multivariable prediction models, namely the Transparent Reporting of a  
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43 143 multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) [20].  
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### 48 49 145 **Study design**

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53 147 A direct observational study which will be conducted prospectively. The preparation and  
54  
55 148 administration of medications by the nurses are directly observed to detect MAEs. This direct  
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57 149 observation study will be disguised to reduce the Hawthorne effect on the observed nurses [15].  
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3 150 The nurses will be informed that the observational study conducted aims to identify strategies  
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5 151 to enhance the medication supply and distribution system and to understand the constraints of  
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8 152 the nurses' working environment and that it is not aimed to assess their personal practices [21].  
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10 153  
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12 154 There are two stages in this study. The first stage is the identification of the predictor variables  
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14 155 while the second stage is the prospective direct observational study. A flowchart of the  
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16 156 development, validation and assessment of the risk prediction model is provided in figure 1.  
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### 21 158 **Study setting**

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26 160 This study is a multicentre, nationwide study which will include Neonatal Intensive Care Units  
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28 161 (NICUs) of five public hospitals which were purposively chosen to reflect the various  
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30 162 categories of public hospitals in terms of specialities.  
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### 34 35 164 **Study outcomes**

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40 166 The outcome of interest in this study is the occurrence of MAEs amongst neonates. MAE is  
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42 167 defined as any deviations during the preparation and administration of medications when  
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44 168 compared to the prescriber's medication order, hospital policies, or the manufacturer's  
45  
46 169 recommendations in the product leaflet [15]. This study intends to focus on the outcome of the  
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48 170 system in place instead of the actions of the individual observed. Hence, this definition will be  
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50 171 employed as it does not focus on the individual's actions.  
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56 173 MAEs are further categorized into subcategories according to the stages of preparation and  
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58 174 administration (Table 1). This will allow us to understand the stages where MAEs occur  
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175 especially since medications for neonates involve multiple manipulations [22]. Definitions of  
 176 the subcategories of MAEs were adopted from various literature [15, 22-24].

177

178 **Table 1** Definitions of subcategory of MAEs

Subcategory of MAEs	Definitions
<i>Preparation</i>	
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.
<i>Administration</i>	
Wrong route	A dose of the correct drug is administered at a site that was not prescribed.

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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 $\pm 15\%$ of the recommended infusion time.

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

183

#### 184 **Data collection**

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

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

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3 199 weight, gender, length of stay), clinical (e.g. ventilation, diagnosis) and medication related  
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5 200 information (e.g. name of medication prescribed, dose, frequency) will be collected using a  
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7 201 predesigned data collection form.  
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12 203 The observer will closely shadow the nurses who has consented to the participation in this  
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14 204 study throughout the medication preparation and administration round. During the observation,  
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16 205 data related to the preparation of the medication (e.g. details of reconstitution and/or dilution  
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18 206 such as the time of preparation, expiry, solvent, diluent), administration of the medication (e.g.  
19  
20 207 time, rate, route, compatibility) and other procedures (e.g. labelling, double checking of  
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22 208 medication administered, interruption and/or distraction) will be recorded. For ethical reasons,  
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24 209 the observers will intervene in a non-judgemental manner if a potentially harmful error is about  
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26 210 to reach a patient. However, this error will be included in the dataset as it is assumed that this  
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28 211 error will reach the patient if it is not intervened by the observer.  
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35 213 After each round of observation, the observer will compare his/her notes with the prescriber's  
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37 214 medication order, hospital policies, manufacturer's recommendations in the product leaflet and  
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39 215 data published in literature to detect errors. Demographics of the nurse (e.g. years of working  
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41 216 experience, level of education) responsible for the preparation and administration of  
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43 217 medications will also be recorded. The clinical pharmacist at the study site will observe 10%  
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45 218 of randomly selected drug preparations and administrations to ensure the validity and accuracy  
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47 219 of the data collected by the observers.  
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53 221 **Eligibility criteria**

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

230

### 231 **Data analysis**

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233 Predictor variables

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

247

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

Candidate predictor	Definition	Variable type	Sources
<i>Administration related variables</i>			
Route of administration	Route of administration for the medication administered to patient (ie. oral, parenteral)	Categorical	SR
Complexity of the medication preparation	<ul style="list-style-type: none"> <li>• One step such as withdrawal of required dose from a ready-to-use preparation</li> <li>• Two step such as reconstitution of a drug which is then followed by the withdrawal of the required dose</li> <li>• 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</li> </ul>	Categorical	SR
<i>Working environment related variables</i>			
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
<i>Patient related variables</i>			
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)

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*Individual related variables*

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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

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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].



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3 262 Model development  
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8 264 The categorization of selected predictor variables into groups will be avoided to minimize the  
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10 265 loss of potentially predictive information [29]. To ensure that there are no outliers, boxplots  
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12 266 and descriptive statistics will be employed to examine continuous variables. Correction to the  
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14 267 values obtained will be done if possible, or otherwise these values will be set to missing.  
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19 269 A univariate analysis will then be conducted to identify the variables significantly associated  
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21 270 with the occurrence of a MAE [30]. Variables with  $p < .25$  will be considered for inclusion into  
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23 271 the multivariable model. A higher significance value is used to overcome a drawback of  
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25 272 univariate analysis where during univariate analysis, individual variables that are weakly  
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27 273 associated with the outcome are overlooked although they may contribute significantly when  
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29 274 combined [30].  
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35 276 The predictor variables will then undergo multivariable logistic regression. Categories with  
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37 277 limited data will be combined to meet the assumptions of regression. Backward stepwise  
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39 278 selection will be used as it is preferred method in selecting the predictors to be included in the  
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41 279 model as compared to forward stepwise selection which has been found to result in a model  
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43 280 where potentially meaningful predictors may have been erroneously trimmed and that may be  
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45 281 difficult to reproduce [31]. Variables will be removed or retained in the model according to its  
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47 282 statistical significance. Statistical significance of  $p < 0.20$  will be conservatively used for  
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49 283 inclusion instead of a small significance level (e.g.  $p < 0.05$ ) to prevent the omission of  
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51 284 important predictor variables and removing less significant variables that may be practically  
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53 285 and clinically relevant [30]. Overfitting models may occur regardless of the choice of a smaller  
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55 286 or larger significance value, especially if a smaller dataset is used. Overfitting models are  
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3 287 models which are too specific to the development sample but are not generalizable in new but  
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5 288 similar individuals. Therefore, we will employ the least absolute shrinkage and selection  
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7 289 operator (LASSO) to reduce overfitting during the model building process [31, 32]. In addition,  
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10 290 subsequent internal validation may also provide insight on the model being unstable or  
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12 291 overfitted [33]. Multicollinearity will also be assessed using the variance inflation factor to  
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14 292 identify predictor variables who have strong correlation with each other [34]. We will then  
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16 293 explore the interactions between variables in the model by adding a new term to the model  
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18 294 when assessing interactions for each two predictors. The interaction effects resulting from the  
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20 295 combination of predictors is determined by the coefficient of this new term.  
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#### 25 26 297 Model performance

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30 299 The model's performance will be evaluated by its calibration and discrimination [35]. The  
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32 300 discriminatory ability of the model which is the ability of the model to differentiate between  
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34 301 patients at risk of MAE and patients who are not at risk, will be assessed using the area under  
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36 302 the receiver operating characteristic (ROC) curve. Calibration is an assessment of the  
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38 303 agreement between observed outcomes in the data and predicted outcomes of the model. It will  
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40 304 be assessed graphically through the inspection of calibration plots and the Hosmer-Lemeshow  
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42 305 test [36].  
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#### 48 49 307 Model validation

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53 309 Internal validation of the prediction model will be assessed using the bootstrapping re-sampling  
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55 310 technique to ensure that the prediction models are reproducible. This will provide insight into  
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57 311 the model potentially being too optimistic or overfitted [37]. Bootstrap samples utilizing at  
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3 312 least 500 bootstrap resampling procedures will be drawn. The difference in the discrimination  
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5 313 and calibration between each bootstrap model and the original model developed will be  
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7 314 averaged to adjust for optimism [32]. Bootstrapping also provides a shrinkage factor which  
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9 315 allow the adjustment of the estimated regression coefficients in the final model overfitting. A  
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11 316 global shrinkage factor of greater than 0.9 is desired [38].  
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17 318 Model presentation18  
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21 320 The final model will be presented for both the derivation and validation samples. As predictions  
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23 321 are the main interest, the full prediction model which consist of the regression coefficients and  
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25 322 the model intercept will be published. Various modes of presentation formats such as a  
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27 323 simplified scoring tool or web-based electronic risk calculators will be considered.  
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33 325 Study progress34  
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37 327 The first stage of the study, which is the identification of the predictor variables while the has  
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39 328 been completed while the second stage which is the prospective direct observational study, is  
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41 329 in progress.  
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47 331 Sample size48  
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51 333 Sample size calculations following the four criteria for binary outcomes recommended by  
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53 334 Riley et al are performed to minimize overfitting and to ensure that precise predictions of the  
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55 335 developed model [39]. We have specified the anticipated outcome proportion as 0.31 [40], a  
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57 336 total number of candidate predictors of 20, a global shrinkage factor of 0.9 and the anticipated  
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3 337 model performance as defined by Cox-Snell  $R^2$  ( $R^2_{CS}$ ) as 0.15 [39]. Taking these criteria into  
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5 338 considerations, the minimum sample size required to ensure all criteria are fulfilled is 1,097  
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7 339 drug administrations.  
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### 11 341 **Ethics and dissemination**

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15 343 This study protocol was approved by the Medical Research and Ethics Committee (MREC),  
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17 344 Ministry of Health Malaysia, with the identification number of NMRR-21-1484-59494 (IIR).  
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19 345 Findings from our study will be disseminated through presentations at scientific conferences  
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21 346 and peer-reviewed publications.  
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33 351 participation in this study.  
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### 38 353 **Contributors**

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40 354 JHB, NMS, AA, NAMT and CMP conceptualised the study. JHB and ZS designed the  
41  
42 355 statistical plan for this study, which was reviewed by all authors. JHB drafted the manuscript,  
43  
44 356 which was reviewed by all authors. All authors read, contributed and approved the final version  
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46 357 of the manuscript.  
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6 363 **Competing interests**  
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8 364 None declared.  
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12 366 **Patient and public involvement**  
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16 368 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination  
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18 369 plans of our research.  
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22 371 **Patient consent for publication**  
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24 372 Not applicable.  
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28 374 **Ethics approval**  
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30 375 This study received ethics approval from the Medical Research and Ethics Committee  
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32 376 (MREC), Ministry of Health Malaysia (NMRR-21-1484-59494 (IIR). Participants provided  
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34 377 written informed consent to be observed in this study.  
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46 382 **Data availability statement**  
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48 383 Data sharing is not applicable since no datasets were generated or analysed in this study.  
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52 385 **Open access**  
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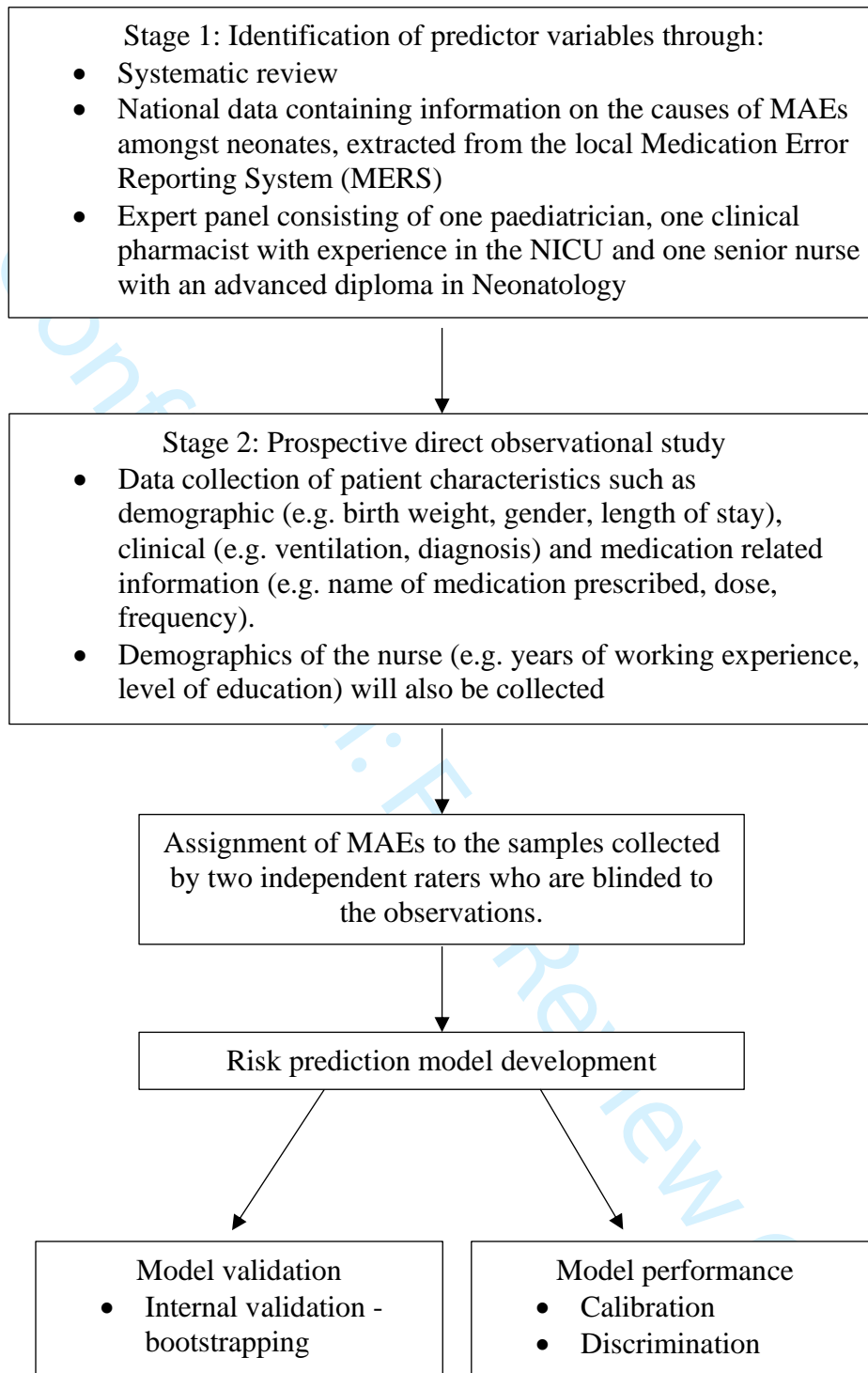
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35 400 **References**36  
37 401

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- 40 402 1. Roughead EE, Semple SJ, Rosenfeld E. The extent of medication errors and adverse
- 
- 41 403 drug reactions throughout the patient journey in acute care in Australia.
- Int J Evid Based*
- 
- 42 404
- Healthc.*
- 2016;14(3):113-22.
- 
- 43
- 
- 44 405 2. Elliott RA, Camacho E, Jankovic D, et al. Economic analysis of the prevalence and
- 
- 45 406 clinical and economic burden of medication error in England.
- BMJ Qual Saf.*
- 2021;30(2):96-
- 
- 46 407 105.
- 
- 47
- 
- 48 408 3. Cousins DH, Gerrett D, Warner B. A review of medication incidents reported to the
- 
- 49 409 National Reporting and Learning System in England and Wales over 6 years (2005-2010).
- Br J*
- 
- 50 410
- Clin Pharmacol.*
- 2012;74(4):597-604.
- 
- 51
- 
- 52 411 4. Cousins DH, Dewsbury C, Matthew L, et al. NPSA Safety in doses: medication safety
- 
- 53 412 incidents in the NHS: the fourth report of the patient safety observatory. London.2007.
- 
- 54
- 
- 55 413 5. Walsh EK, Hansen CR, Sahm LJ, et al. Economic impact of medication error: a
- 
- 56 414 systematic review.
- Pharmacoepidemiol Drug Saf.*
- 2017;26(5):481-97.
- 
- 57
- 
- 58 415 6. Kale A, Keohane CA, Maviglia S, et al. Adverse drug events caused by serious
- 
- 59 416 medication administration errors.
- BMJ Qual Saf.*
- 2012;21(11):933-8.
- 
- 60
- 
- 417 7. Krzyzaniak N, Bajorek B. Medication safety in neonatal care: a review of medication
- 
- 418 errors among neonates.
- Ther Adv Drug Saf.*
- 2016;7(3):102-19.

- 419 8. Kwan JL, Lo L, Sampson M, et al. Medication reconciliation during transitions of care  
420 as a patient safety strategy: a systematic review. *Ann Intern Med.* 2013;158(5 Pt 2):397-403.
- 421 9. Nguyen TL, Leguelinel-Blache G, Kinowski JM, et al. Improving medication safety:  
422 Development and impact of a multivariate model-based strategy to target high-risk patients.  
423 *PLoS One.* 2017;12(2):e0171995.
- 424 10. Ebbens MM, Laar SAV, Wesselink EJ, et al. Prospective Validation of a Risk Prediction  
425 Model to Identify High-Risk Patients for Medication Errors at Hospital Admission. *Ann*  
426 *Pharmacother.* 2018;52(12):1211-17.
- 427 11. Fung L, Huynh T, Brush T, et al. A Correlation of a Medication-Focused Risk Score to  
428 Medication Errors at Discharge. *J Clin Pharmacol.* 2020;60(11):1416-23.
- 429 12. Bonnerup DK, Lisby M, Saedder EA, et al. Risk of prescribing errors in acutely  
430 admitted patients: a pilot study. *Int J Clin Pharm.* 2016;38(5):1157-63.
- 431 13. Saedder EA, Lisby M, Nielsen LP, et al. Detection of Patients at High Risk of  
432 Medication Errors: Development and Validation of an Algorithm. *Basic Clin Pharmacol*  
433 *Toxicol.* 2016;118(2):143-9.
- 434 14. Kang MJ, Jin Y, Jin T, et al. Automated Medication Error Risk Assessment System  
435 (Auto-MERAS). *J Nurs Care Qual.* 2018;33(1):86-93.
- 436 15. Allan EL, Barker KN. Fundamentals of medication error research. *Am J Hosp Pharm.*  
437 1990;47(3):555-71.
- 438 16. Meyer-Massetti C, Cheng CM, Schwappach DL, et al. Systematic review of  
439 medication safety assessment methods. *Am J Health Syst Pharm.* 2011;68(3):227-40.
- 440 17. Henry Basil J, Premakumar CM, Mhd Ali A, et al. Prevalence, Causes and Severity of  
441 Medication Administration Errors in the Neonatal Intensive Care Unit: A Systematic Review  
442 and Meta-Analysis. *Drug Saf.* 2022.
- 443 18. Royston P, Moons KG, Altman DG, et al. Prognosis and prognostic research:  
444 Developing a prognostic model. *BMJ.* 2009;338:b604.
- 445 19. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps  
446 for development and an ABCD for validation. *Eur Heart J.* 2014;35(29):1925-31.
- 447 20. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable  
448 prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement.  
449 *BMJ.* 2015;350:g7594.
- 450 21. van der Veen W, van den Bemt P, Wouters H, et al. Association between  
451 workarounds and medication administration errors in bar-code-assisted medication  
452 administration in hospitals. *J Am Med Inform Assoc.* 2018;25(4):385-92.
- 453 22. McLeod MC, Barber N, Franklin BD. Methodological variations and their effects on  
454 reported medication administration error rates. *BMJ Qual Saf.* 2013;22(4):278-89.
- 455 23. Chedoe I, Molendijk H, Hospes W, et al. The effect of a multifaceted educational  
456 intervention on medication preparation and administration errors in neonatal intensive  
457 care. *Arch Dis Child Fetal Neonatal Ed.* 2012;97(6):F449-55.
- 458 24. ASHP guidelines on preventing medication errors in hospitals. *Am J Hosp Pharm.*  
459 1993;50(2):305-14.
- 460 25. Barker KN, McConnell WE. The problems of detecting medication errors in hospitals.  
461 *Am J Hosp Pharm.* 1962;19:360-9.
- 462 26. Parekh N, Ali K, Davies JG, et al. Medication-related harm in older adults following  
463 hospital discharge: development and validation of a prediction tool. *BMJ Qual Saf.*  
464 2020;29(2):142-53.

- 1  
2  
3 465 27. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview  
4 466 and some applications. *Stat Med*. 1991;10(4):585-98.
- 5 467 28. Leurent B, Gomes M, Faria R, et al. Sensitivity Analysis for Not-at-Random Missing  
6 468 Data in Trial-Based Cost-Effectiveness Analysis: A Tutorial. *Pharmacoeconomics*.  
7 469 2018;36(8):889-901.
- 8 470 29. Steyerberg EW. Clinical Prediction Models. A Practical Approach to Development,  
9 471 Validation and Updating. 1st edition ed. Berlin: Springer; 2009.
- 10 472 30. Hosmer DW, Lemeshow S, Sturdivant RX. Applied logistic regression. New York: John  
11 473 Wiley & Sons, Incorporated,; 2013.
- 12 474 31. Grant SW, Collins GS, Nashef SAM. Statistical Primer: developing and validating a risk  
13 475 prediction model. *Eur J Cardiothorac Surg*. 2018;54(2):203-08.
- 14 476 32. Steyerberg EW. Clinical Prediction Models. 2nd ed ed: Springer Nature Switzerland;  
15 477 2019.
- 16 478 33. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., et al. Prognostic modeling with logistic  
17 479 regression analysis: in search of a sensible strategy in small data sets. *Med Decis Making*.  
18 480 2001;21(1):45-56.
- 19 481 34. Vatcheva KP, Lee M, McCormick JB, et al. Multicollinearity in Regression Analyses  
20 482 Conducted in Epidemiologic Studies. *Epidemiology (Sunnyvale)*. 2016;6(2).
- 21 483 35. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and Calibration of Clinical  
22 484 Prediction Models: Users' Guides to the Medical Literature. *JAMA*. 2017;318(14):1377-84.
- 23 485 36. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction  
24 486 models: a framework for traditional and novel measures. *Epidemiology*. 2010;21(1):128-38.
- 25 487 37. Moons KG, Kengne AP, Woodward M, et al. Risk prediction models: I. Development,  
26 488 internal validation, and assessing the incremental value of a new (bio)marker. *Heart*.  
27 489 2012;98(9):683-90.
- 28 490 38. Harrell FE, Jr. Regression modeling strategies with applications to linear models,  
29 491 logistic regression, and survival analysis. New York: Springer; 2001. p. 45-61.
- 30 492 39. Riley RD, Snell KI, Ensor J, et al. Minimum sample size for developing a multivariable  
31 493 prediction model: PART II - binary and time-to-event outcomes. *Stat Med*. 2019;38(7):1276-  
32 494 96.
- 33 495 40. Raja Lope RJ, Boo NY, Rohana J, et al. A quality assurance study on the  
34 496 administration of medication by nurses in a neonatal intensive care unit. *Singapore Med J*.  
35 497 2009;50(1):68-72.
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**Fig 1** Flowchart of risk prediction model development and validation of medication administration errors (MAEs) in neonates

# BMJ Paediatrics Open

## 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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3 **1 Development and validation of a risk prediction model for medication administration**  
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5 **2 errors amongst neonates in the neonatal intensive care unit: a study protocol**  
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3 **51 ABSTRACT**  
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6 **52**

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8 **53 Introduction**  
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10 **54** Medication administration errors (MAEs) are the most common type of medication error.  
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12 **55** Furthermore, they are more common amongst neonates as compared to adults. MAEs can result  
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14 **56** in severe patient harm, subsequently causing a significant economic burden to the healthcare  
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16 **57** system. Targeting and prioritising neonates at high risk of MAEs is crucial in reducing MAEs.  
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18 **58** To the best of our knowledge, there is no predictive risk score available for the identification  
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20 **59** of neonates at risk of MAEs. Therefore, this study aims to develop and validate a risk prediction  
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22 **60** model to identify neonates at risk of MAEs.  
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28 **62 Methods and analysis**  
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30 **63** This is a prospective direct observational study that will be conducted in five neonatal intensive  
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32 **64** care units. A minimum sample size of 820 drug preparations and administrations will be  
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34 **65** observed. Data including patient characteristics, drug preparation- and administration-related  
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36 **66** information, and other procedures will be recorded. After each round of observation, the  
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38 **67** observers will compare his/her observations with the prescriber's medication order, hospital  
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40 **68** policies and manufacturer's recommendations to determine whether MAE has occurred. To  
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42 **69** ensure reliability, the error identification will be independently performed by two clinical  
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44 **70** pharmacists after the completion of data collection for all study sites. Any disagreements will  
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46 **71** be discussed with the research team for consensus. To reduce overfitting and improve the  
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48 **72** quality of risk predictions, we have pre-specified a priori the analytical plan i.e. prespecifying  
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50 **73** the candidate predictor variables, handling missing data and validation of the developed model.  
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52 **74** The model's performance will also be assessed. Finally, various modes of presentation formats  
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54 **75** such as a simplified scoring tool or web-based electronic risk calculators will be considered.  
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**77 Ethics and dissemination**

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

**84 What is already known on this topic**

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

**93 What this study adds**

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

**98 How this study might affect research, practice, or policy**

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

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3 101 among stakeholders on the need for the implementation of interventions to prevent  
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5 102 MAEs amongst high-risk neonates.  
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Confidential: For Review Only



## 103 INTRODUCTION

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105 Medication errors (MEs) may arise throughout the medication use process which consists of  
106 prescribing, transcribing, dispensing, administration, and monitoring [1]. Medication  
107 administration errors (MAEs) are the most commonly occurring error as compared to  
108 prescribing and dispensing, amounting to more than 50% of all MEs [2, 3]. Furthermore, MAEs  
109 are associated with the highest number of incidents resulting in death and severe harm than  
110 other stages of the medication use process. As a result, they contribute to significant economic  
111 burden from the utilisation of healthcare services [4, 5]. It is estimated that approximately 4,000  
112 hospitalised patients are harmed by a total of six million medication doses administered,  
113 costing between USD25 and 35 million annually in the United States [6]. A systematic review  
114 of all types of MEs reported that the prevalence of MAEs amongst neonates ranged between  
115 31% and 63% as compared to paediatric and adult patients which ranged between 12.8% to  
116 73% and 14.6% to 41% respectively [7].

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118 A key aspect of a successful intervention is targeting and prioritising patients at high risk of  
119 MEs to improve medication safety [8]. Several risk scores have been developed to identify  
120 patients at risk of MEs, either amongst hospitalized adults [9], at admission or during discharge  
121 [10, 11]. Others risk scores specifically identify patients at risk of prescribing errors [12, 13].  
122 The Automated Medication Error Risk Assessment System (Auto-MERAS) [14] was the only  
123 developed and validated tool for the prediction of MAEs. However, it was developed and  
124 validated amongst hospitalised adults based on incident reports extracted from the local safety  
125 reporting system. Although the use of incident reports to measure MAEs may generate rich  
126 information on the causal factors linked to MAEs, it is the least accurate method to measure  
127 MAEs as compared to direct observation and chart review [15, 16]. Apart from that, the use of

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3 128 incident reports meant that major risk factors such as nurses' workload could not be analysed  
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10 131 Given that the prevalence of MAEs amongst neonates has been reported to be as high as 94.9%  
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12 132 [17], a validated model incorporating an extensive list of potential risk factors associated with  
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14 133 MAEs would facilitate the healthcare professionals involved in the medication use process to  
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16 134 identify at-risk neonates in the neonatal intensive care unit (NICU). To the best of our  
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18 135 knowledge, a predictive risk score to identify neonates at risk of MAEs specifically is not yet  
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20 136 available. Therefore, this study aims to develop and internally validate a multivariable  
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22 137 prediction model for the identification of MAEs amongst neonates using a prospective direct  
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24 138 observational study design. The model will also be externally validate by using data from a  
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26 139 different set of neonates. The feasibility of using the risk prediction model for risk stratification  
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28 140 will also be evaluated.  
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## 35 142 **METHODS**

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40 144 This study will be conducted in accordance with the recommendations for model development  
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42 145 and validation [18, 19]. The study protocol will reported based on the checklist for  
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44 146 multivariable prediction models, namely the Transparent Reporting of a multivariable  
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46 147 prediction model for Individual Prognosis Or Diagnosis (TRIPOD) [20].  
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### 50 51 149 **Study design**

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56 151 A direct observational study for the development of the risk prediction model will be conducted  
57  
58 152 prospectively between April 2022 and April 2023. The subsequent development and validation  
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3 153 of the model will be performed until April 2024. The preparation and administration of  
4  
5 154 medications by the nurses are directly observed to detect MAEs. A flowchart of the  
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8 155 development, validation and assessment of the risk prediction model is provided in Figure 1.  
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### 11 12 157 **Study setting**

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17 159 This national-level multicentre study will include the NICUs of five public hospitals. All  
18  
19 160 hospitals under the Ministry of Health Malaysia (MOH) are classified as state hospitals, major  
20  
21 161 specialist hospitals, minor specialist hospitals, or non-specialist hospitals. The subspecialty of  
22  
23 162 neonatology is only available in the state and major specialist hospitals. There are five regions  
24  
25 163 in Malaysia, i.e. Northern, Central, Southern, East Coast, and East Malaysia. One hospital was  
26  
27 164 chosen from each of these regions. The five selected public hospitals consisting of two state  
28  
29 165 hospitals and three major specialist hospitals were purposively chosen to include both  
30  
31 166 categories of public hospitals providing neonatology subspecialty. The total bed capacity of  
32  
33 167 the NICUs in these five public hospitals ranges from 16 to 38 beds.  
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### 39 40 169 **Study outcomes**

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45 171 In this study, the outcome of interest is the occurrence of MAEs amongst neonates. MAE can  
46  
47 172 be defined as any deviations during the preparation and administration of medications when  
48  
49 173 compared to the prescriber's medication order, hospital policies, or the manufacturer's  
50  
51 174 recommendations in the product leaflet [21]. The main intention of this study is to focus on the  
52  
53 175 impact of the outcomes on the system in place instead of the actions of the individual observed.  
54  
55 176 Hence, the above-mentioned definition will be employed as it does not focus on the individual's  
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57  
58 177 actions.  
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178

179 MAEs are further categorized into subcategories according to the stages of preparation and  
 180 administration (Table 1). This will provide a better understanding of the stages where MAEs  
 181 occur, especially since medication preparation for neonates involves multiple manipulations  
 182 [22]. The definitions of the subcategories of MAEs were adopted from various literature [15,  
 183 21, 23] and reviewed by an expert panel consisting of two academicians with at least 20 years  
 184 of experience and two pharmacists with at least 8 years of experience.

185

186 **Table 1** Definitions of the subcategories of MAEs

Subcategory of MAEs	Definitions
<i>Preparation</i>	
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.

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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.
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*Administration*

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Wrong route	A dose of the correct drug is administered at a site that was not prescribed.
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Wrong patient	Administration of a dose of the correct drug to a different patient.
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Incompatibility	Administration of two or more incompatible medications concurrently in the same line without flushing in between the administrations of these medications.
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Wrong rate of administration	A dose of the drug is administered for more than $\pm 15\%$ of the recommended infusion time.
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188 **Data collection**

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190 Two clinical pharmacists with at least ten years of experience will act as observers to conduct  
191 the direct observations. Each round of direct observation will be performed by one observer.

192 The observers will be trained beforehand based on the direct observation method of data  
193 collection as described by Barker and McConnell [24]. They will also be trained to observe  
194 and perform practical exercises on the direct observation technique. They are required to  
195 complete and pass a written examination (score of at least 80%) consisting of video simulations  
196 of drug preparation and administration before they can conduct the observations by themselves.

197 Following that, they will perform pilot observations for three days in the ward to familiarise  
198 themselves with the procedures in the ward and to reduce the Hawthorne effect. The expected

199 number of medication administrations over three days ranges from 80 to 200 medications  
200 prescribed. To ensure a uniform understanding of the data collection procedures, all pilot

201 observations will be discussed with the research team. However, these pilot observations will  
202 not be included as part of the data for this study.

203

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

215

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

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3 227 For ethical reasons, the observers will intervene in a non-judgemental manner if a potentially  
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5 228 harmful error is about to reach the patient. Examples of MAEs that may be potentially harmful  
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8 229 are the administration of a drug that has expired or deteriorated [26] and tenfold overdose [27].  
9  
10 230 In contrast, late in administering doses is not considered to be potentially harmful. In such  
11  
12 231 events, the observers will follow a flowchart that outlines the measures required for an  
13  
14 232 intervention (Figure 2) [28]. However, this error will be included in the dataset as it is assumed  
15  
16  
17 233 that this error will reach the patient if it is not intervened by the observer.  
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19 234

21 235 After each round of observation, the observer will compare his/her notes with the prescriber's  
22  
23 236 medication order, hospital policies, manufacturer's recommendations in the product leaflet,  
24  
25 237 and data published in the literature to detect possible MAEs. Demographics of the nurse (e.g.  
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27  
28 238 years of working experience and level of education) responsible for the preparation and  
29  
30 239 administration of medications will also be recorded. In addition, the clinical pharmacist at each  
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32 240 study site will conveniently select and observe 10% [29, 30] of drug preparations and  
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34 241 administrations to ensure the validity and accuracy of the data collected by the observers. The  
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37 242 observation will then be compared with the data collected by the observers. All observations  
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39 243 by the clinical pharmacist and the observer must be identical for the data to be considered valid  
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42 244 and accurate.  
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46 246 Error identification will be independently and individually performed by two clinical  
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48 247 pharmacists with at least six years of clinical experience. The two clinical pharmacists are not  
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50 248 involved in the data collection of the direct observational study. Moreover, they will be  
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53 249 performing the assignment of errors to the samples collected separately to avoid influencing  
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55 250 each other's decisions. Disagreements encountered during the assignment of errors to the  
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58 251 observed samples will be discussed with the research team to reach a consensus.  
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5 253 **Eligibility criteria**6  
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8 255 Medications prepared and administered by nurses for all routes of administrations will be  
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10 256 included while excluded medication administrations are (1) those administered by parents, (2)  
11  
12 257 enteral feedings, parenteral nutrition and blood-derived products, (3) omission of medication  
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14 258 administration because patient is not present in the ward during medication administration  
15  
16 259 rounds, (4) omissions due to clinical reasons such as those determined by the nurses (e.g.  
17  
18 260 contraindications) and lack of intravenous access, (5) rectal administrations; when neonatal-  
19  
20 261 specific rectal dosage forms are unavailable and the available paediatric rectal dosage form is  
21  
22 262 modified to a lower dose, and (6) medical gases and dietary supplements. The same inclusion  
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24 263 and exclusion criteria will be applied to the validation cohort.  
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33 265 **Data analysis**34  
35 26636  
37 267 Predictor variables38  
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42 269 To develop a comprehensive method for identifying neonates at risk of MAEs, a total of 13  
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44 270 candidate predictor variables have been identified through the following sources: (1) an  
45  
46 271 extensive systematic review conducted to evaluate the available literature on the factors  
47  
48 272 associated with MAEs amongst neonates [17], (2) national data containing information on the  
49  
50 273 causes of MAEs amongst neonates, extracted from the Medication Error Reporting System  
51  
52 274 (MERS) through the MOH Pharmaceutical Services Programme; and (3) expert panel. The  
53  
54 275 expert panel consists of a paediatrician with 14 years of clinical experience, a clinical  
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56 276 pharmacist with 15 years of clinical experience, and a senior nurse with an advanced diploma  
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3 277 in Neonatology and 20 years of clinical experience. The expert panel was established to review  
4  
5 278 the predictor variables gathered from the literature review and to identify other important  
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7  
8 279 predictor variables based on their clinical experience. Based on the systematic review, MERS,  
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10 280 and the expert panel, the identified candidate predictor variables are categorised and defined as  
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12 281 presented in online supplemental table S1.  
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17 283 Missing data18  
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21 285 Although the predictors included in our data collection are not expected to have a considerable  
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23 286 amount of missing data, some will inevitably occur. Hence, strategies to deal with missing data  
24  
25 287 will be determined based on the predictors. Predictors with more than 20% missing data will  
26  
27 288 be excluded [31]. Multiple imputations by chained equations will be performed to impute  
28  
29 289 missing values for predictors with data missing at random. For each predictor variable, five  
30  
31 290 multiple imputation datasets will be created to obtain an overall estimate as recommended by  
32  
33 291 Rubin and Schenker [32]. Lastly, a sensitivity analysis using the pattern-mixture model  
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35 292 approach will be employed to ensure that the data is not missing at random [33].  
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42 294 Model development43  
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46 296 The two strategies available for the development of a model are the full model and stepwise  
47  
48 297 selection. In our study, the full model approach described by Harrell [34] where all identified  
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50 298 candidate predictor variables will be included in the model regardless of their association with  
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52 299 MAEs or influence on model performance will be conducted. Stepwise selection will then be  
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54 300 performed and the results will be compared with the full model. The best model produced by  
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3 301 these strategies will then be chosen based on the best fit, the accuracy of the model and the  
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5 302 model with the least error.  
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10 304 The categorisation of selected predictor variables into groups will be avoided to minimise the  
11  
12 305 loss of potentially predictive information [35]. The frequency distributions for categorical  
13  
14 306 predictor variables will be examined and categories with less than six observations will be  
15  
16 307 combined [34]. Since the outcome in our study is categorical, a binary logistic regression will  
17  
18 308 be performed. The regression coefficients will be estimated using maximum likelihood  
19  
20 309 estimation (MLE), a probabilistic framework for estimating the model parameters. All the  
21  
22 310 necessary assumptions for regression will be checked. The use of both the full model and  
23  
24 311 stepwise selection is common. However, with the use of real data, certain assumptions such as  
25  
26 312 multicollinearity may not be fulfilled. In instances where such assumptions are not met, the  
27  
28 313 model developed may produce large variations, leading to poor regression coefficient estimates  
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30 314 and overfitting.  
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37 316 Overfitting models are models that are too specific for the development sample, making them  
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39 317 less generalisable for new but similar individuals. Considering the possibility of having an  
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41 318 overfitted model, the least absolute shrinkage and selection operator (LASSO) binary logistic  
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43 319 regression will be performed. LASSO is a method that penalises the model coefficients to select  
44  
45 320 predictors and to reduce overfitting during the model-building process [36, 37]. In LASSO, a  
46  
47 321 first-order penalty function will be constructed to shrink the regression coefficients of the  
48  
49 322 predictor variables to a certain range. A regularisation factor, lambda ( $\lambda$ ) will be chosen to  
50  
51 323 maximise the out-of-sample model fit by applying a penalty to shrink the regression  
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53 324 coefficients. Predictor variables with a regression coefficient of zero will be removed from the  
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325 model, leaving behind a panel of optimal variables. Therefore, predictor variables with a weak  
326 association with the model will be excluded to ensure that all coefficients are optimised.

327

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

331

332 Model performance

333

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

348

349 Model validation

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5 351 Internal validation of the prediction model will be assessed using the bootstrapping re-sampling  
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7 352 technique to ensure that the prediction models are reproducible. This will provide insight as to  
8  
9 353 whether the model is potentially too optimistic or overfitted [38]. Bootstrap samples utilising  
10  
11 354 at least 500 bootstrap resampling procedures will be drawn. The difference in the  
12  
13 355 discrimination and calibration between each bootstrap model and the original model developed  
14  
15 356 will be averaged out to adjust for optimism [36]. Bootstrapping also provides a shrinkage factor  
16  
17 357 that allows the adjustment of the estimated regression coefficients in the final model. A global  
18  
19 358 shrinkage factor of greater than 0.9 is desired [34]. The external validation of the new risk  
20  
21 359 prediction model will be conducted to demonstrated its predictive value. It will be conducted  
22  
23 360 prospectively among new patients who are similar to those recruited for the development of  
24  
25 361 the risk prediction model. The predictive performance based on the same measures of  
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27 362 discrimination and calibration used in the internal validation will be reported.  
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35 364 Model presentation36  
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39 366 The final model will be presented for both the derivation and validation samples. As predictions  
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41 367 are the main interest, the full prediction model that consist of the regression coefficients and  
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43 368 the model intercept will be published. Various modes of presentation formats such as a  
44  
45 369 simplified scoring tool or web-based electronic risk calculators will be considered.  
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51 371 Sample size52  
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55 373 Sample size calculations following the four criteria for binary outcomes as recommended by  
56  
57 374 Riley et al. are performed to minimise overfitting of the model and to ensure that precise  
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3 375 predictions of the developed model [39]. We have specified the anticipated outcome proportion  
4  
5 376 as 0.31 [40], a total number of candidate predictors of 15, a global shrinkage factor of 0.9 and  
6  
7  
8 377 the anticipated model performance as 0.15 as defined by Cox-Snell  $R^2$  ( $R^2_{CS}$ ) [39]. Taking these  
9  
10 378 criteria into consideration, the minimum sample size required to ensure all criteria are fulfilled  
11  
12 379 is 820 drug administrations. Each sample of drug administration is considered an independent  
13  
14 380 sample even if it is prepared and administered by the same nurse as the factors leading to an  
15  
16 381 MAE may be different. The number of drug administrations to be observed in the study sites  
17  
18  
19 382 will be allocated proportionally to the number of expected admissions in each hospital.  
20  
21  
22 383

### 23 384 **Ethics and dissemination**

24 385

25  
26 386 This study protocol was approved by the Medical Research and Ethics Committee (MREC),  
27  
28 387 Ministry of Health Malaysia (NMRR-21-1484-59494 [IIR]) on 24<sup>th</sup> January 2022 and the  
29  
30 388 Medical Ethics Committee, Universiti Kebangsaan Malaysia on 10<sup>th</sup> February 2022. Findings  
31  
32 389 from our study will be disseminated through presentations at scientific conferences and peer-  
33  
34 390 reviewed publications.  
35  
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40 391

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54 397

### 55 398 **Contributors**

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1  
2  
3 399 JHB, NMS, AA, NAMT and CMP conceptualised the study. JHB and ZS designed the  
4  
5 400 statistical plan for this study, which was reviewed by all authors. JHB drafted the manuscript  
6  
7 401 and all authors reviewed manuscript. All authors read, contributed and approved the final  
8  
9 402 version of the manuscript.  
10  
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20  
21

22 407

#### 24 408 **Competing interests**

26 409 None declared.  
27  
28

29 410

#### 31 411 **Patient and public involvement**

32 412

35 413 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination  
36  
37 414 plans of this research.  
38  
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40 415

#### 42 416 **Patient consent for publication**

44 417 Not applicable.  
45  
46

47 418

#### 49 419 **Ethics approval**

51 420 This study received ethical approval from the Medical Research and Ethics Committee  
52  
53 421 (MREC), Ministry of Health Malaysia (NMRR-21-1484-59494 [IIR]) on 24<sup>th</sup> January 2022  
54  
55 422 and the Medical Ethics Committee, Universiti Kebangsaan Malaysia on 10<sup>th</sup> February 2022.  
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3 424 **Provenance and peer review**  
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5 425 Not commissioned; externally peer-reviewed.  
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8 426

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10 427 **Data availability statement**  
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12 428 Data sharing is not applicable since no datasets were generated or analysed in this study.  
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15 429

16  
17 430 **Open access**  
18

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25 434 provided the original work is properly cited, appropriate credit is given, any changes made  
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46  
47  
48  
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50  
51 445 **References**  
52

53  
54 446

- 55  
56 447 1. Roughead EE, Semple SJ, Rosenfeld E. The extent of medication errors and adverse  
57 448 drug reactions throughout the patient journey in acute care in Australia. *Int J Evid Based*  
58 449 *Healthc.* 2016;14(3):113-22.  
59  
60

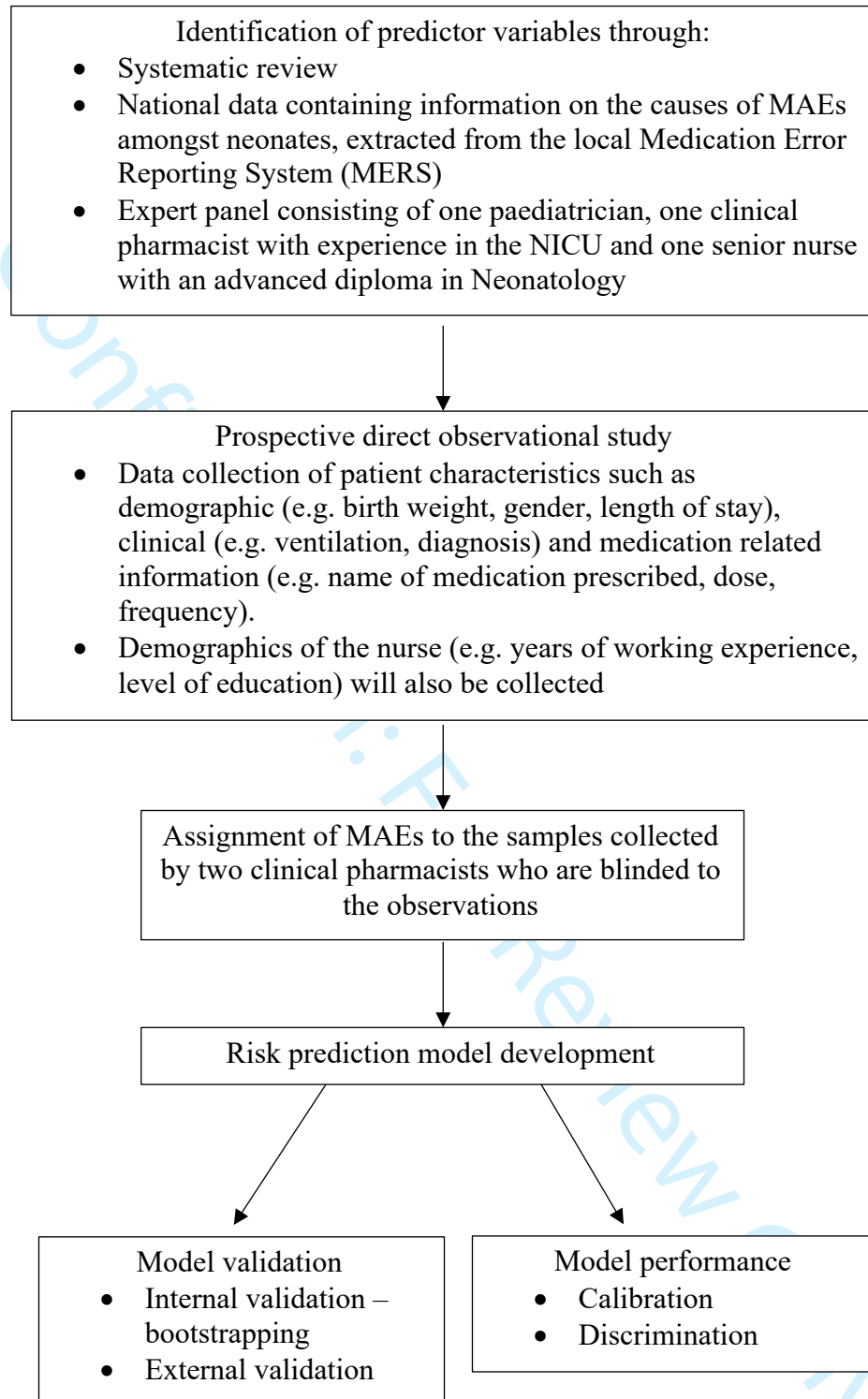
- 1  
2  
3 450 2. Elliott RA, Camacho E, Jankovic D, et al. Economic analysis of the prevalence and  
4 451 clinical and economic burden of medication error in England. *BMJ Qual Saf.* 2021;30(2):96-  
5 452 105.
- 7 453 3. Cousins DH, Gerrett D, Warner B. A review of medication incidents reported to the  
8 454 National Reporting and Learning System in England and Wales over 6 years (2005-2010). *Br J*  
9 455 *Clin Pharmacol.* 2012;74(4):597-604.
- 11 456 4. Cousins DH, Dewsbury C, Matthew L, et al. NPSA Safety in doses: medication safety  
12 457 incidents in the NHS: the fourth report of the patient safety observatory. London.2007.
- 13 458 5. Walsh EK, Hansen CR, Sahm LJ, et al. Economic impact of medication error: a  
14 459 systematic review. *Pharmacoepidemiol Drug Saf.* 2017;26(5):481-97.
- 16 460 6. Kale A, Keohane CA, Maviglia S, et al. Adverse drug events caused by serious  
17 461 medication administration errors. *BMJ Qual Saf.* 2012;21(11):933-8.
- 18 462 7. Krzyzaniak N, Bajorek B. Medication safety in neonatal care: a review of medication  
19 463 errors among neonates. *Ther Adv Drug Saf.* 2016;7(3):102-19.
- 21 464 8. Kwan JL, Lo L, Sampson M, et al. Medication reconciliation during transitions of care  
22 465 as a patient safety strategy: a systematic review. *Ann Intern Med.* 2013;158(5 Pt 2):397-403.
- 23 466 9. Nguyen TL, Leguelinel-Blache G, Kinowski JM, et al. Improving medication safety:  
24 467 Development and impact of a multivariate model-based strategy to target high-risk patients.  
25 468 *PLoS One.* 2017;12(2):e0171995.
- 27 469 10. Ebbens MM, Laar SAV, Wesselink EJ, et al. Prospective Validation of a Risk Prediction  
28 470 Model to Identify High-Risk Patients for Medication Errors at Hospital Admission. *Ann*  
29 471 *Pharmacother.* 2018;52(12):1211-17.
- 31 472 11. Fung L, Huynh T, Brush T, et al. A Correlation of a Medication-Focused Risk Score to  
32 473 Medication Errors at Discharge. *J Clin Pharmacol.* 2020;60(11):1416-23.
- 33 474 12. Bonnerup DK, Lisby M, Saedder EA, et al. Risk of prescribing errors in acutely  
34 475 admitted patients: a pilot study. *Int J Clin Pharm.* 2016;38(5):1157-63.
- 35 476 13. Saedder EA, Lisby M, Nielsen LP, et al. Detection of Patients at High Risk of  
36 477 Medication Errors: Development and Validation of an Algorithm. *Basic Clin Pharmacol*  
37 478 *Toxicol.* 2016;118(2):143-9.
- 39 479 14. Kang MJ, Jin Y, Jin T, et al. Automated Medication Error Risk Assessment System  
40 480 (Auto-MERAS). *J Nurs Care Qual.* 2018;33(1):86-93.
- 41 481 15. Allan EL, Barker KN. Fundamentals of medication error research. *Am J Hosp Pharm.*  
42 482 1990;47(3):555-71.
- 43 483 16. Meyer-Massetti C, Cheng CM, Schwappach DL, et al. Systematic review of  
44 484 medication safety assessment methods. *Am J Health Syst Pharm.* 2011;68(3):227-40.
- 46 485 17. Henry Basil J, Premakumar CM, Mhd Ali A, et al. Prevalence, Causes and Severity of  
47 486 Medication Administration Errors in the Neonatal Intensive Care Unit: A Systematic Review  
48 487 and Meta-Analysis. *Drug Saf.* 2022;45(12):1457-76.
- 49 488 18. Royston P, Moons KG, Altman DG, et al. Prognosis and prognostic research:  
51 489 Developing a prognostic model. *BMJ.* 2009;338:b604.
- 52 490 19. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps  
53 491 for development and an ABCD for validation. *Eur Heart J.* 2014;35(29):1925-31.
- 54 492 20. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable  
55 493 prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement.  
56 494 *BMJ.* 2015;350:g7594.



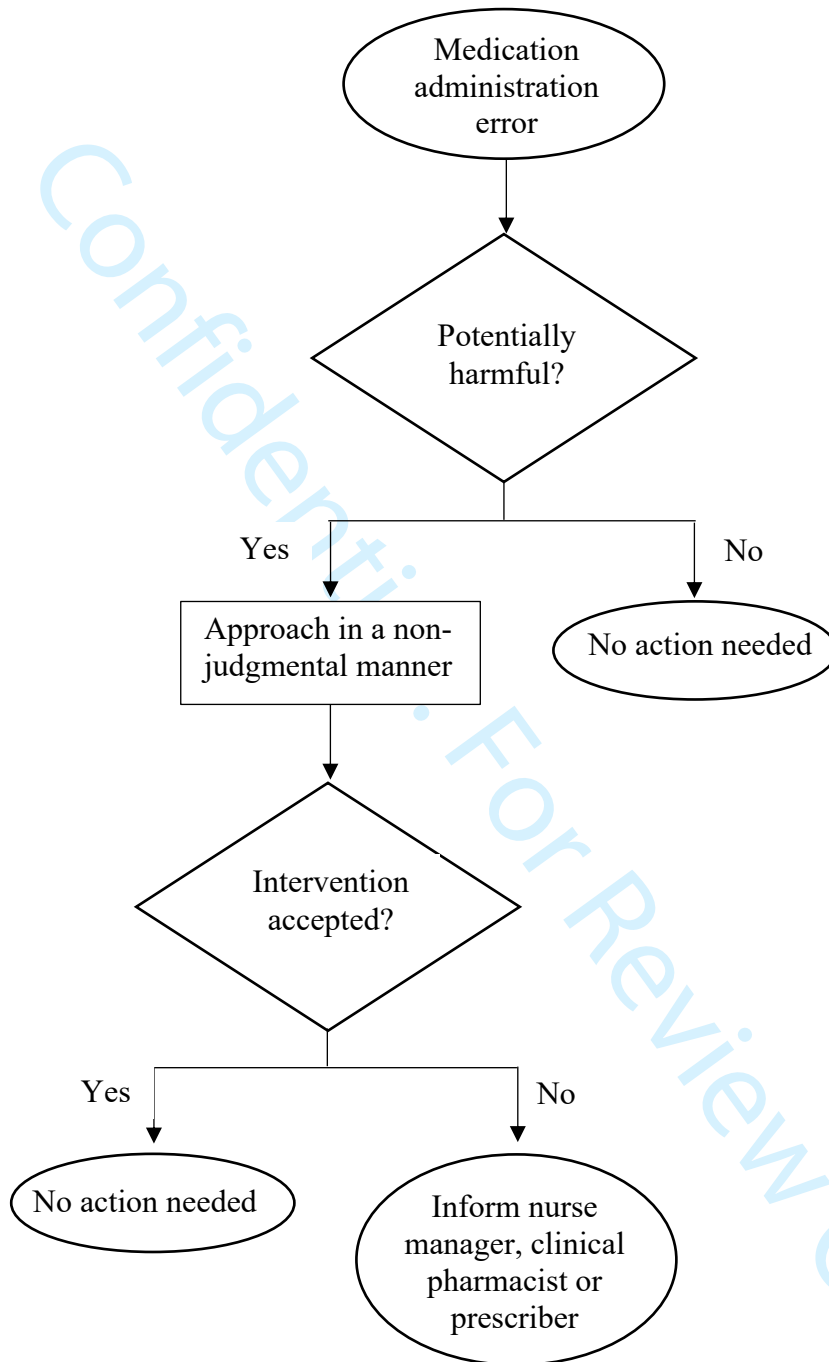
- 1  
2  
3 495 21. Chedoe I, Molendijk H, Hospes W, et al. The effect of a multifaceted educational  
4 496 intervention on medication preparation and administration errors in neonatal intensive  
5 497 care. *Arch Dis Child Fetal Neonatal Ed.* 2012;97(6):F449-55.
- 7 498 22. McLeod MC, Barber N, Franklin BD. Methodological variations and their effects on  
8 499 reported medication administration error rates. *BMJ Qual Saf.* 2013;22(4):278-89.
- 9 500 23. ASHP guidelines on preventing medication errors in hospitals. *Am J Hosp Pharm.*  
10 501 1993;50(2):305-14.
- 12 502 24. Barker KN, McConnell WE. The problems of detecting medication errors in hospitals.  
13 503 *Am J Hosp Pharm.* 1962;19:360-9.
- 14 504 25. van der Veen W, van den Bemt P, Wouters H, et al. Association between  
15 505 workarounds and medication administration errors in bar-code-assisted medication  
16 506 administration in hospitals. *J Am Med Inform Assoc.* 2018;25(4):385-92.
- 18 507 26. Ramirez-Camacho M, Ake N, Gloria A, et al. Medication errors of intravenous therapy  
19 508 in the neonatal intensive care unit of a second-level hospital in southeastern Mexico. *Latin*  
20 509 *American Journal of Pharmacy.* 2020;39(3):604-11.
- 22 510 27. Doherty C, Mc Donnell C. Tenfold medication errors: 5 years' experience at a  
23 511 university-affiliated pediatric hospital. *Pediatrics.* 2012;129(5):916-24.
- 24 512 28. Westbrook JI, Li L, Raban MZ, et al. Associations between double-checking and  
25 513 medication administration errors: a direct observational study of paediatric inpatients. *BMJ*  
26 514 *Qual Saf.* 2021;30(4):320-30.
- 28 515 29. Potts AL, Barr FE, Gregory DF, et al. Computerized physician order entry and  
29 516 medication errors in a pediatric critical care unit. *Pediatrics.* 2004;113(1 Pt 1):59-63.
- 30 517 30. Kadmon G, Bron-Harlev E, Nahum E, et al. Computerized order entry with limited  
31 518 decision support to prevent prescription errors in a PICU. *Pediatrics.* 2009;124(3):935-40.
- 33 519 31. Parekh N, Ali K, Davies JG, et al. Medication-related harm in older adults following  
34 520 hospital discharge: development and validation of a prediction tool. *BMJ Qual Saf.*  
35 521 2020;29(2):142-53.
- 36 522 32. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview  
37 523 and some applications. *Stat Med.* 1991;10(4):585-98.
- 39 524 33. Leurent B, Gomes M, Faria R, et al. Sensitivity Analysis for Not-at-Random Missing  
40 525 Data in Trial-Based Cost-Effectiveness Analysis: A Tutorial. *Pharmacoeconomics.*  
41 526 2018;36(8):889-901.
- 42 527 34. Harrell FE, Jr. Regression modeling strategies: with applications to linear models,  
43 528 logistic and ordinal regression and survival analysis: Springer; 2015.
- 45 529 35. Steyerberg EW. Clinical Prediction Models. A Practical Approach to Development,  
46 530 Validation and Updating. 1st edition ed. Berline: Springer; 2009.
- 47 531 36. Steyerberg EW. Clinical Prediction Models. 2nd ed ed: Springer Nature Switzerland;  
48 532 2019.
- 49 533 37. Grant SW, Collins GS, Nashef SAM. Statistical Primer: developing and validating a risk  
50 534 prediction model. *Eur J Cardiothorac Surg.* 2018;54(2):203-08.
- 52 535 38. Moons KG, Kengne AP, Woodward M, et al. Risk prediction models: I. Development,  
53 536 internal validation, and assessing the incremental value of a new (bio)marker. *Heart.*  
54 537 2012;98(9):683-90.
- 56 538 39. Riley RD, Snell KI, Ensor J, et al. Minimum sample size for developing a multivariable  
57 539 prediction model: PART II - binary and time-to-event outcomes. *Stat Med.* 2019;38(7):1276-  
58 540 96.
- 59  
60

1  
2  
3 541 40. Raja Lope RJ, Boo NY, Rohana J, et al. A quality assurance study on the  
4 542 administration of medication by nurses in a neonatal intensive care unit. *Singapore Med J.*  
5 543 2009;50(1):68-72.  
6 544  
7  
8  
9  
10  
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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
<i>Administration-related variables</i>				
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
<i>Workin- environment related variables</i>				
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 [17:00-07:59])	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

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*Patient-related variables*

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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

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*Individual-related variables*

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Working experience in NICU	Total number of years employed as a nurse in a NICU	Continuous	years	Expert panel
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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, advanced 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

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MERS = medication error reporting system, SR = systematic review