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Association between workarounds and medication administration errors in bar-code-assisted medication administration in hospitals

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ABSTRACT

Objective: To study the association of workarounds with medication administration errors using barcode-assisted medication administration (BCMA), and to determine the frequency and types of workarounds and medication administration errors.

Materials and Methods: A prospective observational study in Dutch hospitals using BCMA to administer medication. Direct observation was used to collect data. Primary outcome measure was the proportion of medication administrations with one or more medication administration errors. Secondary outcome was the frequency and types of workarounds and medication administration errors. Univariate and multivariate multilevel logistic regression analysis were used to assess the association between workarounds and medication administration errors. Descriptive statistics were used for the secondary outcomes.

Results: We included 5793 medication administrations for 1230 inpatients. Workarounds were associated with medication administration errors (adjusted odds ratio 3.06 [95% CI: 2.49-3.78]). Most commonly, procedural workarounds were observed, such as not scanning at all (36%), not scanning patients because they did not wear a wristband (28%), incorrect medication scanning, multiple medication scanning, and ignoring alert signals (11%). Common types of medication administration errors were omissions (78%), administration of non-ordered drugs (8.0%), and wrong doses given (6.0%).

Discussion: Workarounds are associated with medication administration errors in hospitals using BCMA. These data suggest that BCMA needs more post-implementation evaluation if it is to achieve the intended benefits for medication safety.

Conclusion: In hospitals using barcode-assisted medication administration, workarounds occurred in 66% of medication administrations and were associated with large numbers of medication administration errors.

Key words: safety, medication administration errors, quality of care, BCMA
BACKGROUND AND SIGNIFICANCE

Many hospitals have implemented information technology (IT)-based systems, such as computerized physician order entry systems (CPOEs), to reduce prescribing errors.1–5 Also, hospitals have implemented electronic barcode-assisted medication administration (BCMA) systems to reduce medication administration errors.6–11 BCMA systems work by scanning both the barcode on the medication package and the barcode on the patient’s identification wristband to attempt to achieve the “five rights” of medication administration: right patient, right medication, right dose, right route, and right time. Several studies have shown reductions in medication administration errors after the introduction of a BCMA system.12–16

However, IT systems such as BCMA are not always used as intended or instructed, and so-called workarounds can occur.17–20 A workaround is a (temporary) method for achieving a task when the usual or planned method is not working. In IT, a workaround is often used to deal with hardware, programming, or communication problems. Kobayashi et al.21 defined workarounds as “informal temporary practices for handling exceptions to normal workflow.” Cresswell et al.22 studied workarounds in the process of CPOE in several hospitals. They found 12 types of workarounds, including use of paper, use of print screens, use of word processors, and use of electronic shortcuts. Koppel et al.19 documented 15 types of workarounds associated with BCMA systems, such as affixing patients’ barcoded identification wristbands to computer carts and carrying several patients’ prescanned medications on carts. Furthermore, 31 causes of these workarounds were documented, such as malfunctioning scanners, unreadable or missing patient identification wristbands, medications without barcodes, failing scanner batteries, and uncertain and unstable wireless connectivity. The issue with workarounds is that if they are frequently used, they may decrease or eliminate the potential benefits of technology. Research on workarounds in the BCMA process has been focused mostly on qualitative descriptions of the range and types of workarounds.22–25 Little research has been done to quantify the frequency of workarounds in the BCMA process or to explore their potential consequences.

OBJECTIVE

To determine the association of workarounds with medication administration errors. Secondary objectives were to determine the frequency and types of workarounds and the frequency and types of medication administration errors.

MATERIALS AND METHODS

Study design

We performed a multicenter prospective observational study in adult patients admitted to hospitals exclusively using BCMA in the medication administration process. The regional medical ethics committee (Regionale Medisch Ethische Commissie Zorgpartners Friesland) approved the study protocol. The study was registered in the Dutch trial register with trial ID NTR4355. Study data were coded to ensure the privacy of the participants. A detailed version of the study protocol has been published.26

Participants

Patients from the internal medicine (including cardiology, pulmonary diseases, and geriatrics), neurological diseases, and surgical wards of 4 Dutch hospitals operating BCMA to administer medications were included. Only patients ≥18 years of age were included.

Definitions and classification

We defined workarounds according to Kobayashi et al.,21 as “informal temporary practices for handling exceptions to normal workflow” for the specific ward. Workarounds were defined as deviations from the BCMA standard operating procedures of each study ward. We classified workarounds using a self-developed classification system, which is derived from the system of Koppel et al.19 Workarounds were caused by blockades in the nurses’ workflow. We classified 6 categories of blockades. These were related to (1) procedures in general (such as not scanning at all); (2) the patient wristband/identification process (such as unreadable wristband or patient sleeping/not in the room, or wristband detached from patient); (3) the medication scanning process (such as medication not barcoded); (4) computer- or scanner-based blockades (such as computer or scanner down or defective); (5) the nurse workflow—the nurse stops medication administration based on a distraction/disturbance (such as a nurse being disturbed in the case of standard operating procedures clearly stating that the nurse should not respond to distracting situations); and (6) other blockades in the administration process (such as no proper medication in the cart). Categories were mutually exclusive; for example, if a workaround was classified as procedural, it was not also classified as not scanning the medication.

A medication administration error was defined as “a deviation from the physician’s medication order as entered in the electronic patient medication record,” derived from Allan and Barker.27 We excluded time-window errors and intravenous and nonintravenous preparation errors, because these errors are not preventable by BCMA and are thus unlikely to be influenced by workarounds in the BCMA process.

The types of medication administration errors were classified using the system of Van den Bemt et al.,28 omission (drug prescribed, but not administered), unordered (drug administered, but not prescribed), wrong dosage form (dosage form administered to patient deviated from prescribed dosage form), wrong route of administration, wrong administration technique, wrong dosage (dosage too high or low), and other errors. We excluded time-window errors, as these are mostly perceived as nonserious.

Setting

All included hospitals had implemented CPOE and BCMA. A variety of software is used for both the CPOE and the BCMA. As a consequence, procedures for prescribing and administering medications differed among hospitals. Medication administration procedures within a hospital varied slightly between wards because of differences in patient groups or tasks. The included hospitals used barcode-labeled unit dose systems for medications distribution to inpatients. In the pharmacy departments, pharmacy technicians dispensed barcode-labeled medication sachets for individual patients in trays labeled with the patient’s name and barcode. Trays were placed in medication carts, which were delivered to the wards once a day (or more frequently). Wards did not have ward-based medication stock (except emergency medication). In general, there were 4 scheduled medication administration rounds per day in the participating hospitals: 6–10 a.m., 10 a.m.–2 p.m., 6–8 p.m., and 8–10 p.m. One nurse was responsible for medication administration for one administration round per ward. Nurse trainees were supervised by registered nurses. During a drug administration round, nurses selected the
prescribed medication(s) for each inpatient from the prefilled trays. In addition to the cart, nurses also took along the computer or the workstation on wheels to access the BCMA system. The BCMA systems in use checked concordance between patient, administered drug, and prescription. Inpatients did not use their own (out-hospital-prescribed) medications. More details can be found in the published protocol.26

Outcome measures
The primary outcome measure of the study was the proportion of medications given to a patient with one or more medication administration errors. For this outcome, the association with the occurrence of one or more workarounds was studied.

Secondary outcomes were the frequency and types of workarounds and the frequency and types of medication administration errors in the BCMA process.

Covariates
Factors likely to influence the association between workarounds and medication administration errors were included in our analysis. The following factors were considered: hospital/BCMA characteristics (time after implementation of BCMA in the hospital), type of ward, day of the week, dispensing time for the medication rounds, medication characteristics (Anatomic Therapeutic Chemical [ATC] code medication, drug administration route), and number of medicines per patient per round. These covariates were selected based on the research of Schimmel et al.29 and van den Bemt et al.30 their known or theoretical associations with the outcomes, and their availability in the dataset.

Data collection
The disguised observation method was used to collect data on medication administrations and workarounds. Three trained observers, all pharmacy undergraduate students, accompanied the nurses and observed them while they administered medications during their regular planned rounds. The observers were supervised by the researchers and a local hospital pharmacist. To prevent nurses from adjusting their behavior due to the presence of the observer, the observer was introduced as a person intended to monitor the performance of the medication distribution system on that ward in general.

Before data collection, the observer set up an observation schedule. Observational rounds were selected randomly out of all the regular medication distribution rounds of a specific ward. During a 5-month observation period per hospital, at least 3 rounds were observed each day of the week, with a weekly minimum of 21 medication administration rounds.

In practice, the observer accompanied the nurse, who administered medications using BCMA, and observed and recorded details of the administration of each dose of medication to patients. In case an observer was aware of a potentially serious error, he or she intervened for ethical reasons, but the error was included in the dataset. If the observer was not able to see the detailed medication administration, this was noted, and these data were discarded.

After each observed medication administration round, a computer printout of the prescribed medications for all patients for that round was collected from the hospital’s electronic patient records. Subsequently, observation records were compared with prescribed medications to identify medication administration errors. Observation records were also compared with the standard operation procedures of the BCMA process for that specific nursing department, to identify workarounds.

Training of the observers
Observers were trained by studying relevant literature on observational techniques,31–42 doing practical exercises on observing techniques, and completing a theoretical written exam. The observers needed to pass the exam by scoring 8 out of 10 points and had 2 chances to pass, to be able to observe. Observers studied the standard operating procedures for drug administration and the BCMA systems of the nursing departments. Each observer performed pilot observations for 1 week on 1 nursing department to become familiar with the BCMA process. Pilot observations were discussed with the research team to ensure consistency in definitions and data collection procedures among observers. Pilot data were discarded.

Sample size calculation
Prior studies on the effect of BCMA showed a substantial reduction in errors (about 30%) after the implementation of BCMA (from 14.4% [4743 errors in 32 972 observations] to 9.9% [2651 errors in 26 892 observations]).7,9,16,41 The nearly 10% error rate was a mix of all resulting errors, including those caused by workarounds.

The purpose of the sample size calculation was to estimate the number of observations needed to reject the null hypothesis, stating that there was no association between workarounds and medication administration errors, with a power of 90%. We assumed that 8% of medication administrations per patient per nurse resulted in a workaround. We also assumed that the frequency of medication administration errors following a workaround was 2-fold higher compared with the situation without a workaround, resulting in a relative risk of 2.

With alpha = 0.05 and a power of 0.9, we needed to observe 1500 medication administrations per hospital to reject the null hypothesis.

Data monitoring
All data were entered into an Access database (v. 2010, Microsoft). Ten percent of entered data were checked by a second researcher. If data entry errors were found, additional portions of 10% of the data were checked, until no errors were found within a portion. Passwords secured access to the research databases. Before data analysis, the final database was locked.

Statistical analysis
Medication administration errors were dichotomized as 1 (≥1 one errors) or 0 (no errors). The association between one or more workarounds and the occurrence of one or more medication administration errors was analyzed using logistic mixed models. In all models, we included a random intercept to account for the potential dependence of observations, as most of the time more than one observation was made by the same nurse. First, a crude analysis was performed, and additionally an adjusted analysis in which we adjusted for hospital, type of nursing department, day of the week, dispensing time, number of drugs per round, and route of administration as the independent variables.

Mixed model analyses were conducted with MLwiN version 6.3 and all other analyses with SPSS version 23.0.
RESULTS

Primary outcomes
In the 4 participating hospitals, we observed 6021 medication administrations overall. A total of 228 (3.8%) were excluded because of inconsistencies or because the observer could not see the administration in detail. The observers did not have to intervene to prevent potentially serious errors. We included 5793 medication administrations for 1230 patients (Table 1). In 3633 medication administrations (63%), one or more workarounds were observed, and of those, 299 (8.2%) were erroneous. In the remaining 2160 (37%), we did not observe workarounds. In these medication administrations, 16 (0.7%) were erroneous. The occurrence of 2 or more medication administration errors was rare (0.07% of all observations). Baseline characteristics of 5793 observed medication administrations in the analyses are presented in Table 2. In both the crude and adjusted analyses, we found a statistically significant association between workarounds and medication administration errors (crude odds ratio [OR]: 3.14, 95% CI: 2.52-3.92, and adjusted OR 3.06, 95% CI: 2.49-3.78; Table 3).

Secondary outcomes
Procedural workarounds (such as not scanning at all) were most common (n = 1307, 36%). Other workarounds concerned patient scanning (such as no barcode wristband on the patient) (n = 1017, 28%) and medication scanning (including scanning before actual administration, scanning medication for more than one patient at a time, and ignoring alerts) (n = 400, 11%). Common types of medication administration errors were omissions (n = 233, 78%), administration of unordered drugs (24, 8.0%), and wrong doses given (18, 6.0%) (Table 4).

DISCUSSION
We found a significant association between workarounds and medication administration errors in hospitals using BCMA technology. Nurses did not use the BCMA technology as intended in more than two-thirds of drug administrations, and this increased the risk of medication administration errors.

The high frequency of workarounds in our study is in line with the findings of Rack et al.17 and Koppel et al.19 Likewise, our medication administration error rate is similar to rates reported in recent systematic reviews (Barker et al.43 and Keers et al.44), although most of the included studies did not evaluate BCMA systems. Only a few studies focused specifically on BCMA systems. In a more recent but small study, Hardmeier et al.45 found 5% medication administration errors, including time-window errors, while using BCMA. This study was performed in a children’s hospital and included 300 observations.

The strength of this study is that it provides quantitative information about workarounds and their possible association with medication administration errors, as one of the first such studies worldwide. Other strengths are the multicenter design, which enhances its generalizability, and the robust method of data collection by disguised observation. The study also has some limitations. Although disguised observation is considered to be the best method for data collection in medication administration error studies,37,42,46,47 observation bias may still occur. The process of medication administration is often very fast. We trained the observers to stay close to the nurse administering the medication and to observe every single administration in detail. Only a small number of observations had to be discarded because the observers could not collect all necessary data for a medication administration. Observers may have paid closer attention to detect a medication administration error when they observed a workaround. We trained the observers carefully, however, and used standard definitions. Observers may also have become tired and therefore less accurate and could have made random errors. Observers worked solo; it would have been better to perform observations by 2 observers, but the necessary staffing for this was not available. The observations may have influenced the nurses, but from the literature, we know this effect (the Hawthorne effect48) tends to be small. Furthermore, a recent Australian study provides evidence that health care workers such as nurses do not alter their activities based on the presence of an observer.32 Notwithstanding all our precautions, due to the inherent limitations of disguised observation, errors may have occurred. However, we believe these errors to be random in the sense that they were unlikely to have occurred more often in the presence than the absence of a workaround.

Using disguised observation as a source of data also comes with some ethical issues.41 One of the ethical questions that can be raised is whether observers have the right to observe persons who are not aware of their presence or tasks. After all, the observers were unknown to the patients and not introduced to them. However, patients were not disturbed and did not experience any discomfort caused by the observations. In addition to the national permission for this study, every participating hospital was informed and received copies of the research protocol and the nationwide approval of our research, and no objection was noted. Finally, this research was carried out in internal medicine and surgical hospital nursing departments. Although these nursing departments cover a broad range of patient categories, our findings may not be generalizable to other nursing departments.

We developed a classification system for blockades and resulting workarounds derived from Koppel et al.19 We found more “procedural blockades” and “other blockades in medication administration” than expected. Furthermore, we found large differences between hospitals in frequency and types of workarounds.

| Table 1. Characteristics of observed medication administrations per hospital |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristics  | Hospital 1     | Hospital 2     | Hospital 3     | Hospital 4     | Total          |
| Number of observed patients | 310           | 380           | 297           | 243           | 1230           |
| Number of observed nurses | 83            | 69            | 72            | 48            | 272            |
| Number of observed medication administrations | 1528         | 1757          | 1497          | 1011          | 5793           |
| Number of observed workarounds | 523           | 925           | 1315          | 870           | 3633           |
| Number of medication administration errors in administrations without a workaround | 18            | 156           | 32            | 93            | 299            |
| Number of medication administration errors in administrations with a workaround | 0             | 6             | 0             | 10            | 16             |
### Table 2. Baseline characteristics of 5793 observed medication administrations

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Category</th>
<th>One or more medication administration errors in administrations with one or more workarounds (in total of 3633), n (%)</th>
<th>One or more medication administration errors in administrations without workarounds (in total of 2160), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>Hospital 1</td>
<td>17 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>BCMA since 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital 2</td>
<td>156 (52)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td></td>
<td>BCMA since 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital 3</td>
<td>30 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>BCMA since 2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital 4</td>
<td>93 (31)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td></td>
<td>BCMA since 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Nursing Department</td>
<td>Cardiology</td>
<td>42 (14)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td></td>
<td>Pulmonology Medicine</td>
<td>23 (8)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td></td>
<td>Geriatrics</td>
<td>21 (7)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td></td>
<td>General Internal Medicine</td>
<td>39 (13)</td>
<td>1 (6.25)</td>
</tr>
<tr>
<td></td>
<td>Neurology</td>
<td>28 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>85 (29)</td>
<td>5 (31.25)</td>
</tr>
<tr>
<td></td>
<td>Orthopedics</td>
<td>24 (8)</td>
<td>1 (6.25)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>34 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Day of the Week</td>
<td>Monday</td>
<td>42 (14)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td></td>
<td>Tuesday</td>
<td>57 (19)</td>
<td>2 (12.50)</td>
</tr>
<tr>
<td></td>
<td>Wednesday</td>
<td>39 (13)</td>
<td>5 (31.25)</td>
</tr>
<tr>
<td></td>
<td>Thursday</td>
<td>47 (16)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td></td>
<td>Friday</td>
<td>54 (19)</td>
<td>1 (6.25)</td>
</tr>
<tr>
<td></td>
<td>Saturday</td>
<td>30 (10)</td>
<td>2 (12.50)</td>
</tr>
<tr>
<td></td>
<td>Sunday</td>
<td>27 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Schedule in 24 h</td>
<td>06–10</td>
<td>124 (42)</td>
<td>6 (37.50)</td>
</tr>
<tr>
<td></td>
<td>10–14</td>
<td>21 (7)</td>
<td>1 (6.25)</td>
</tr>
<tr>
<td></td>
<td>14–18</td>
<td>90 (30)</td>
<td>8 (50.00)</td>
</tr>
<tr>
<td></td>
<td>18–22</td>
<td>61 (21)</td>
<td>1 (6.25)</td>
</tr>
<tr>
<td>ATC</td>
<td>A</td>
<td>79 (27)</td>
<td>5 (31.25)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>19 (6)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>25 (8)</td>
<td>1 (6.25)</td>
</tr>
<tr>
<td></td>
<td>J</td>
<td>10 (3)</td>
<td>2 (12.50)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>14 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>93 (33)</td>
<td>2 (12.50)</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>16 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>18 (6)</td>
<td>1 (6.25)</td>
</tr>
<tr>
<td></td>
<td>Other (D,G,H,I,L,P,V,Y,Z)</td>
<td>79 (27)</td>
<td>2 (12.50)</td>
</tr>
<tr>
<td>Number of Drugs per Patient per Round</td>
<td>1</td>
<td>139 (47)</td>
<td>5 (31.25)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>37 (12)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>120 (41)</td>
<td>8 (50.00)</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
<td>216 (73)</td>
<td>13 (81.25)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>80 (27)</td>
<td>3 (18.75)</td>
</tr>
</tbody>
</table>

*More than one medication administration error in 3 observed workarounds.

### Table 3. Univariate and multivariate analyses of 5793 observed medication administrations

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication administration errors, n (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>Adjusted for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 workarounds</td>
<td>16 (0.28)</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Hospital, type of nursing department, day of the week, schedule in 24 h, ATC, number of drugs per round, route of administration</td>
</tr>
<tr>
<td>1 or &gt;1 workaround(s)</td>
<td>296 (5.11)</td>
<td>3.14 (2.52-3.92)</td>
<td>3.06 (2.49-3.78)</td>
<td></td>
</tr>
</tbody>
</table>

Ref. = reference category.
and medication administration errors. These may be due to differences in the software systems and in training in using BCMA systems. This will be an interesting topic for future research. In some hospitals, the nurses hardly used the scanner unit of the BCMA system. Informal conversations with nursing staff in those hospitals suggested that they may have had insufficient instruction on how to use the scanners; also, scanners were considered to be clumsy to use. In other hospitals, we observed the following practical problems: the medication carts and the computer on wheels including the scanner were too large to roll into some of the patients’ rooms, and therefore they remained in the hallway. In these cases, workarounds seemed to be established and had become accepted practice for how to use the BCMA system. Investigating the reasons for accepting the workarounds and how to overcome these problems needs more work. Furthermore, in the case of, for example, poor software system design, users of these systems could be forced to perform workarounds to prevent patient harm, which is an interesting topic for future research as well.

Hence the reason we observed so many workarounds in our research (in line with earlier findings) is unclear and deserves additional research. The BCMA techniques did not seem to fit well with the daily workflow of nurses who faced both hardware and software blockades. Health care IT systems should be well designed and properly implemented, and match the daily workflow, knowledge, and culture of users. In the system design process of information technology, the future users of these systems should be taken into account. Poor human-machine interface may increase the chance that health care workers will face workflow obstacles and use workarounds. Performing prospective risk analyses before implementing health care information technology could be one solution. One study showed a trend toward more user satisfaction with the information technology system in hospitals using prospective risk analyses, and this may enhance proper use of the system. Others used the Theoretical Domains Framework to identify barriers to appropriate use of technology. Also, the correct and intended use of information technology systems such as BCMA does not stop after implementation of that system and software. Not only do the system and software need to have a correct fit with the daily workflow of the users, but intensive training and retraining of users is also needed so they can use information technology as intended to prevent patient harm. These results have several implications. They suggest that every institution should track the frequency of workarounds, at least initially after implementation of BCMA, and then intervene to try to reduce their frequency. Also, our study results may be used to develop training programs to provide solutions for the problems that lead to workarounds.

**CONCLUSION**

In hospitals using barcode-assisted medication administration, workarounds occurred in two-thirds of medication administrations and were associated with a large number of medication administration errors. These data suggest that BCMA needs more post-implementation evaluation if it is to achieve its intended benefits for medication safety.

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CONTRIBUTORS
WvdV, PMLAvdB, and KT contributed equally to the design, analysis, and interpretation of the data of the study and drafted the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. HW, JWT, DWB, and HJdG made equally substantial contributions to the analysis and interpretation of the data of the study and the drafting of the final manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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