Pharmaceutical care in surgical patients: Tools for measurement and intervention

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A TARGETED METHOD FOR STANDARDIZED ASSESSMENT OF ADVERSE DRUG EVENTS IN SURGICAL PATIENTS

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ABSTRACT

Objectives
This study demonstrates the development, reliability and outcome of a targeted method for standardized assessment of adverse drug events (ADEs) in surgical patients.

Methods
Initial practice evaluation of this ADE assessment method was carried out in a prospective single centre cohort study. In total, 262 electively admitted surgical patients were included. The surgical trigger tool was applied to patients’ medical records by two independent reviewers, and subsequent assessment of causality, severity and preventability of ADEs was carried out by two independent expert panels consisting of a consultant surgeon and a clinical pharmacologist. The surgical trigger tool and causality assessment method were each tested on reliability in a separate group of 50 randomly selected patients using Fleiss and Cohen’s kappa statistics and percentages of agreement. Comparison of this method with an existing trigger tool method for ADEs was performed.

Results
Our surgical trigger tool contains 51 triggers. The inter- and intra-rater calculations showed substantial to almost perfect levels of agreement (kappa range 0.71–0.83), with a 97.8–98.5% percentage of agreement. Fair to substantial levels of agreement were calculated for causality, severity and preventability (kappa range 0.38–0.79). The percentages of inter- and intra-rater agreement were 68.9% and 70.5% for causality, 67.0% and 82.0% for severity, and both 98.4% for preventability, respectively. Compared with the existing trigger tool method for ADEs, we found an additional 363 triggers, 18 ADEs (an extra 20%) and 3 preventable ADEs in our surgical cohort.

Conclusions
This targeted trigger tool for standardized assessment of ADEs in surgical patients shows excellent agreement between reviewers. The assessment of medication-related harm had acceptable agreement. Compared with an existing ADE trigger tool method, the present method found almost 20% extra ADEs. This method can be a useful alternative to existing trigger tool methods, in particular to assess medication safety in surgical patients.
**INTRODUCTION**

Medication-related complications are a frequent type of in-hospital adverse events (AEs; 19%)\(^1\). Medication-related AEs are widely known as adverse drug events (ADEs)\(^2\). These events remain a serious problem in hospitals. The reported proportion of hospitalized patients with ADEs varies from 1.6 to 41.4%. Many ADEs, potentially 15–59%, can be avoided\(^3\).

In hospitals, surgical patients are not only at risk for AEs related to surgical procedures (40%) but also for complications due to the use of medication (15%)\(^4\). First, medications often related to ADEs are frequently used in the surgical population\(^5\)–\(^7\). Second, transfers along the surgical pathway, with related handovers and errors in communication, are likely to be relevant in A(De)E occurrence\(^8\). In contrast to medical patients, surgical patients are physically transferred from the admission ward to various locations such as holding area (prep ward) before surgery, operating room, recovery room or ICU, and back to a hospital ward. Each location has different caregivers as well as medication decisions for various reasons related to a surgical intervention\(^4\).

Because of the recent introduction of strategies and/or guidelines to improve patient safety and medication safety in surgical patients\(^9\), there is a growing demand for methods to quantify and monitor the impact of these changes. A standardized method to detect, assess and classify medication-related harm in specifically surgical patients and to evaluate the effect of medication safety improvements in surgical patients has not yet been developed.

Several methods have been described to detect ADEs, such as voluntary reporting systems, direct observation and complete record reviews\(^10\)–\(^12\). These methods have different benefits and disadvantages in efficiently and accurately quantifying drug-related problems\(^12\). A gold standard for detecting ADEs does not exist. However, a widely used and accepted detection method is the trigger tool method\(^13\). The primary advantage of the trigger tool method is the more efficient and less labour-intensive quantification of drug-related problems, such as ADEs, compared with other detection methods\(^12\)–\(^14\). The trigger tool method identifies adverse (drug) events based on ‘triggers’ or clues in the patients’ medical record. This method was described by the Institute for Healthcare Improvement (IHI) to detect adverse (drug) events in a variety of medical in- and outpatient populations\(^15\).

Changes in medication are frequently necessary before and after a surgical procedure, such as temporarily stopping anticoagulative therapy pre-operatively. AEs, such as gastrointestinal events and haemorrhage, can be highly associated with medication in medical patients\(^16\). In surgical patients, such events often occur due to the surgical procedure itself\(^17\)–\(^18\). Consequently, few triggers present in the existing trigger tool for ADEs\(^19\) would detect unnecessary potential medication-related harm, such as the trigger ‘abrupt medication stop’. Furthermore, triggers identifying AEs\(^20\) and ADEs in especially surgical patients are lacking. This would introduce under-detection of potential surgical ADEs, which is undesirable in evaluating the effect of medication safety improvements. In the present study, we evaluate that a novel surgical trigger tool as an alternative to the existing trigger tool developed to detect ADEs in medical patients\(^19\) is less appropriate for surgical patients.

A mere trigger tool does not include a critical appraisal of the causal relationship between the found ‘trigger’ and medication. A review and interpretation of an individual case is crucial for
identifying the presence of an ADE and its impact. Several methods of causality assessment have been described. These methods can be divided into three categories: expert judgement, algorithms and probabilistic methods\(^{2}\). Here, we describe the development and testing of a targeted standardized method that incorporates a specified trigger tool to detect surgical ADEs and an expert judgement method to assess the causality, severity and preventability of detected ADEs in surgical patients. Furthermore, we describe outcome on triggers and ADEs of applying this assessment method on a surgical cohort.

**METHODS**

**Development of the surgical ADE assessment method**

To ensure the detailed and individual assessment of ADEs, the targeted method must comprise a surgical trigger tool to screen medical records for ADEs. The causality, severity and preventability of detected ADEs should be established with a causality assessment method based on expert judgement. The aim of the assessment method is to measure medication-related harm due to medication safety improvements in surgery. Hence, reproducible results are of utmost importance to allow comparisons between the different measurements of ADEs. For instance, this method can be used to detect a possible reduction in avoidable medication-related harm by structural interventions of clinical pharmacists\(^{22}\). The overall criteria for the development of a surgical ADE assessment method were as follows:

- efficient, standardized and reproducible retrospective measurement method;
- specific to the surgical population; and
- measurement of ADEs before and after future clinical pharmacy interventions.

**Development of the surgical trigger tool**

First, several previously described trigger tools\(^{2,10,11,16,19,20,23}\) were evaluated for their usefulness in surgical patients. In addition, several triggers were developed based on expert opinion. To gain efficiency and standardization, a few selection criteria for the triggers were defined as follows:

- triggers with an assumed high potential for ADEs in surgical patients;
- triggers related to events occurring during hospitalization;
- triggers related to frequently occurring problems in surgical patients (e.g. pain or thrombosis or bleeding);
- triggers related to harm that occurs sporadically, but with severe consequences (e.g. ototoxicity caused by gentamycin);
- triggers that are relatively easy to detect from the patients’ medical records; and
- triggers related to potential ADEs that can be preferably influenced by direct clinical pharmacy interventions.

The definitive selection of triggers was based on expert consensus, which was obtained from a consultant surgeon and a clinical pharmacologist.
Development of the surgical causality assessment method

Numerous methods have been described for assessing the causal relationship between medication and an AE. These methods have both advantages and disadvantages; however, no single method is universally accepted\textsuperscript{21,24}. Therefore, it is desirable to develop a standardized method that combines expert judgement with algorithm tools to detect ADEs in surgical patients. Furthermore, standardization might have a positive impact on reproducibility and inter- and intra-rater agreement\textsuperscript{21,25}. To enhance standardization and efficiency, the starting point to determine a causal relationship between medication and an AE were the triggers found in the patients’ medical records. The next step of the assessment was to determine the severity of the harm caused by the ADE, followed by determining the preventability of the ADE. If the occurrence of the ADE was the result of a medication error, the ADE was considered to be preventable.

Reliability

The developed targeted method needed to be consistent and reproducible to measure ADEs in surgical patients. Therefore, testing the reliability of the method was essential. To demonstrate the added value of the present trigger tool, we performed a retrospective comparison on our surgical cohort with an existing trigger tool for ADEs\textsuperscript{19}.

Population

The total surgical cohort consisted of 262 patients electively admitted for more than 48 hours between March and June 2009 on three surgical wards at the Academic Medical Centre in Amsterdam, The Netherlands. If a patient was transferred from another ward within the same hospital or previously included in the study, the patient was excluded. The cohort comprised predominantly of gastrointestinal surgery and vascular surgery patients. This cohort of 262 patients was evaluated with the ADE assessment method. To assess the reliability of the method, 50 patients were randomly selected from the cohort to test the surgical trigger tool and another 50 patients with one or more triggers were selected to test the causality assessment. The number of patients was chosen as a representative sample of the surgical population\textsuperscript{23}.

Reliability of the surgical trigger tool

Because there is no gold standard to measure ADEs, the accuracy of the trigger tool method can only be measured by comparing the number of ADEs found with the trigger tool with the number of ADEs found by screening the patients’ complete medical records without the trigger tool\textsuperscript{26,27}. However, both methods are retrospective and susceptible to information bias; thus, the actual number of ADEs remains unclear. Therefore, we chose to determine the reproducibility (i.e. inter- and intra-rater agreement) of this surgical trigger tool to test its use.
Cohen’s kappa coefficient was used to determine inter- and intra-rater agreement. The Fleiss kappa statistic was used to determine agreement among multiple reviewers. The following standards were used to evaluate the strength of the kappa value: ≤ 0 = poor; 0.01–0.20 = slight; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; and 0.81–1 = almost perfect agreement. Here, inter-rater agreement in detecting triggers was determined among three reviewers and between pairs of reviewers. The reviewers had different backgrounds (i.e. doctor or pharmacist) but were trained before independently applying the surgical trigger tool to the test patients. The intra-rater agreement was determined with one reviewer on two separate occasions. The second review of the medical records was approximately one year after the first review. The latter review was conducted to determine the reproducibility of applying the surgical trigger tool to the medical records and to reduce or eliminate bias through recollection by memory of the patients’ medical records. The percentages of agreement among the reviewers were calculated.

Reliability of the surgical causality assessment method

In this study, the causality assessment of potential ADEs found with the surgical trigger tool was executed by two expert panels. Each panel consisted of a consultant surgeon and a clinical pharmacologist. The experts first performed individual and independent assessments. If disagreement between the experts within one panel was present, they held a meeting in which they reached a consensus on causality, severity and preventability.

For each patient, the experts received information regarding positive triggers with extra collected information from the patients’ medical records about the trigger, demographics, laboratory results, the medication list during hospitalization and the discharge letter. Thus, the experts did not receive the complete medical records. This method was chosen to improve the standardization and efficiency of the assessment method.

The reliability of the inter- and intra-rater agreement between the expert panels was calculated by comparing the assessed presence, severity and preventability of the ADEs. We considered the assessment of a probable/possible occurrence of an ADE as the actual presence of an ADE. Agreement in the severity assessment was only calculated for the ADEs that received consensus. The severity category ‘mild’ was compared with the severity categories ‘moderate’ and ‘severe’. For the intra-rater agreement, one expert panel assessed the same patients on a separate occasion, approximately one year after their first causality assessment. Agreement was calculated using Cohen’s kappa coefficient. The percentages of agreement among the expert panels were also calculated.

Outcome assessment

The surgical cohort of 262 patients was assessed with the surgical trigger tool and assessment method on ADEs, preventability and severity. Also, medication accountable for ADEs was assessed. These are classified according to the Anatomical Therapeutic Chemical (ATC) classification of the
World Health Organization (WHO)\textsuperscript{32}. To compensate for an actual validation of the trigger tool, we performed a retrospective comparison on this surgical cohort with an existing trigger tool for ADEs by Rozich et al.\textsuperscript{19}. This comparison was performed by retrospectively evaluating which triggers were adapted and added in the surgical trigger tool. Furthermore, results on triggers, ADEs and preventable ADEs found with the surgical trigger tool compared with Rozich’s trigger tool were demonstrated for the added triggers.

RESULTS

Development of the surgical ADE assessment method

To measure the ADEs in the surgical population, a surgical targeted assessment method incorporating a surgical trigger tool and causality assessment method with expert judgement was developed (Fig. 1).

Development of the surgical trigger tool

A total of 51 triggers were selected for inclusion in the surgical trigger tool (listed in Tables 1a & b). Several of the previously described triggers were defined more explicitly to enhance the applicability and efficiency of the method in the surgical population. Other triggers were based on expert opinion.

Triggers related to events before and after admission or medication-related admissions were redefined or not included. For example, a frequently found AE related to medication is gastrointestinal ulcer/bleeding due to the use of NSAIDs\textsuperscript{33}. We included the triggers ‘newly diagnosed peptic ulcer’ and ‘post-operative gastroscopy’. These triggers were focus-restricted to hospitalization (‘newly diagnosed’/‘post-operative’) to avoid detecting ADEs that took place in the home situation and led to admission. Another example of an explicitly defined trigger was ‘abrupt medication stop with a documented adverse event’. Most trigger tools only use ‘abrupt medication stop’ as a trigger\textsuperscript{19,23}; however, during surgical patients’ hospital stay, intentional abrupt medication stops occur frequently. Defining this trigger more explicitly would result in greater efficiency in detecting ADEs. In contrast, the trigger ‘post-operative electrocardiogram (ECG)’ had not been previously described, but was judged to be applicable to the surgical population due to cardiovascular complications after surgery which might have been provoked by errors with cardiovascular medication. The triggers were divided into practical categories: diagnosis, event, laboratory and medication.
**Surgical patients**

Surgical Trigger Tool on medical records

- No triggers scored → No ADE
- ≥ 1 triggers scored → Potential ADE

Causality assessment by expert panel (individual)

- Agreement → No ADE
- No agreement → Causality assessment by expert panel (consensus)

ADE

- Severity assessment by expert panel
- Preventability assessment by expert panel

- No medication error → Non-preventable ADE
- Medication error → Preventable ADE

Mild

Moderate

Severe

Life-threatening or disabling

Death

**Figure 1. Flowchart Surgical Adverse Drug Event Assessment Method**
<table>
<thead>
<tr>
<th>No.</th>
<th>Trigger</th>
<th>No.</th>
<th>Trigger</th>
<th>No.</th>
<th>Trigger</th>
<th>No.</th>
<th>Trigger</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anaphylactic shock&lt;sup&gt;2&lt;/sup&gt;</td>
<td>13</td>
<td>Abrupt medication stop&lt;sup&gt;19,23&lt;/sup&gt; with a documented AE&lt;sup&gt;*&lt;/sup&gt;</td>
<td>24</td>
<td>Abrupt Hemoglobin drop of 25% or more&lt;sup&gt;21,22&lt;/sup&gt; &gt;24h post-operative&lt;sup&gt;*&lt;/sup&gt;</td>
<td>36</td>
<td>Flumazenil&lt;sup&gt;11,23&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Exacerbation COPD/Asthma&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>14</td>
<td>Blood pressure systolic &lt; 80 mmHg&lt;sup&gt;21,22&lt;/sup&gt;</td>
<td>25</td>
<td>aPTT &gt;100 seconds&lt;sup&gt;19,23&lt;/sup&gt;</td>
<td>37</td>
<td>Antidiarrhoeal&lt;sup&gt;6,20&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Hepatotoxicity&lt;sup&gt;1&lt;/sup&gt;</td>
<td>15</td>
<td>Blood transfusion&lt;sup&gt;16,23&lt;/sup&gt;</td>
<td>26</td>
<td>Request for faeces culture of Clostridium Difficile&lt;sup&gt;23,19,23&lt;/sup&gt;</td>
<td>38</td>
<td>Anti-emetics&lt;sup&gt;19,23&lt;/sup&gt; &gt;48h post-operative&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>All kinds of infections&lt;sup&gt;21,23&lt;/sup&gt; &gt; 72h post-operative&lt;sup&gt;*&lt;/sup&gt;</td>
<td>16</td>
<td>Electrocardiography post-operative&lt;sup&gt;*&lt;/sup&gt;</td>
<td>27</td>
<td>Hyperglycaemia&lt;sup&gt;2&lt;/sup&gt; (&gt;20 mmol/L)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>39</td>
<td>Protrombin complex&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Seizure&lt;sup&gt;3,33&lt;/sup&gt;</td>
<td>17</td>
<td>Gastroscopy&lt;sup&gt;2&lt;/sup&gt; post-operative&lt;sup&gt;*&lt;/sup&gt;</td>
<td>28</td>
<td>Hypoglycaemia (2.8 mmol/L)&lt;sup&gt;23,19,23&lt;/sup&gt;</td>
<td>40</td>
<td>Tranexamic acid&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Myocardial ischemia&lt;sup&gt;20,33&lt;/sup&gt;</td>
<td>18</td>
<td>Interdisciplinary consultation&lt;sup&gt;20,23&lt;/sup&gt;</td>
<td>29</td>
<td>Raised hepatic levels: ALP&lt;sup&gt;19,23&lt;/sup&gt; &gt;34 umol/L&lt;sup&gt;1,4,4,6&lt;/sup&gt;</td>
<td>41</td>
<td>(Nor)epinephrine&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Newly diagnosed* peptic ulcer&lt;sup&gt;2,33&lt;/sup&gt;</td>
<td>19</td>
<td>Newly started anticoagulation therapy&lt;sup&gt;*&lt;/sup&gt;</td>
<td>30</td>
<td>Hyperkalaemia&lt;sup&gt;2,8&lt;/sup&gt; &gt;5 mmol/L</td>
<td>42</td>
<td>Glucose&lt;sup&gt;2&lt;/sup&gt; &gt;5%</td>
</tr>
<tr>
<td>8</td>
<td>Nephrotoxicity&lt;sup&gt;24&lt;/sup&gt;</td>
<td>20</td>
<td>Death&lt;sup&gt;2,23&lt;/sup&gt;</td>
<td>31</td>
<td>Hypokalaemia&lt;sup&gt;2,8&lt;/sup&gt; &lt;2.5 mmol/L</td>
<td>43</td>
<td>Vitamin K&lt;sup&gt;2,8,13,19,23&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>Otoxicity&lt;sup&gt;*&lt;/sup&gt;</td>
<td>21</td>
<td>Unplanned transfer to ICU&lt;sup&gt;20&lt;/sup&gt;/CCU/&lt;sup&gt;33&lt;/sup&gt;/MCU&lt;sup&gt;19,23&lt;/sup&gt; post-operative&lt;sup&gt;23&lt;/sup&gt;</td>
<td>32</td>
<td>INR &gt;3&lt;sup&gt;20,19,23&lt;/sup&gt;</td>
<td>44</td>
<td>Desmopressin&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>Bleeding&lt;sup&gt;2&lt;/sup&gt; post-operative&lt;sup&gt;*&lt;/sup&gt;</td>
<td>22</td>
<td>Postponed operation&lt;sup&gt;*&lt;/sup&gt;</td>
<td>33</td>
<td>Creatinine &gt;100 µmol/L&lt;sup&gt;11,19,23&lt;/sup&gt; and more than doubled&lt;sup&gt;22,33&lt;/sup&gt;</td>
<td>45</td>
<td>Naloxone&lt;sup&gt;19,20,23&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>New rash&lt;sup&gt;20,23&lt;/sup&gt;/urticaria&lt;sup&gt;2&lt;/sup&gt;</td>
<td>23</td>
<td>Patient fall&lt;sup&gt;22&lt;/sup&gt;/lethargy&lt;sup&gt;20,23&lt;/sup&gt;/oversedation&lt;sup&gt;19,23&lt;/sup&gt;</td>
<td>34</td>
<td>Leukocytes &lt; 3x10&lt;sup&gt;9&lt;/sup&gt;/L&lt;sup&gt;20,19&lt;/sup&gt;</td>
<td>46</td>
<td>Eptacog alfa, activated*</td>
</tr>
<tr>
<td>12</td>
<td>Thrombo-embolic complication&lt;sup&gt;20,23,33&lt;/sup&gt;</td>
<td>24</td>
<td>Positive blood culture&lt;sup&gt;20,23&lt;/sup&gt; during use of antibiotics</td>
<td>35</td>
<td></td>
<td>47</td>
<td>Protamin&lt;sup&gt;19,6&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>25</td>
<td></td>
<td>36</td>
<td></td>
<td>48</td>
<td>Resonium®&lt;sup&gt;20,19,23&lt;/sup&gt;/Sorbisten®&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td></td>
<td>37</td>
<td></td>
<td>49</td>
<td>Start antihistamine&lt;sup&gt;20,23,19,23&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27</td>
<td></td>
<td>38</td>
<td></td>
<td>50</td>
<td>Start antimycoticum&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td></td>
<td>39</td>
<td></td>
<td>51</td>
<td>Medication levels (table 2)&lt;sup&gt;2,10,11,16,19,23&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Expert opinion, COPD=Chronic Obstructive Pulmonary Disease, AE=Adverse event, ICU=Intensive Care Unit, CCU=Cardiac Care Unit, MCU=Medium Care Unit, aPTT=Activated Partial Thromboplastin Time, ALP=Alkaline phosphatase, ALT=Alanine transaminase, AST=Aspartate transaminase, INR=international normalised ratio.
### Table 1b. Medication levels for the surgical trigger tool

<table>
<thead>
<tr>
<th>Medication</th>
<th>Medium</th>
<th>Trigger</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Serum</td>
<td>If deviant from reference</td>
<td>Low level &lt;4 mg/L, top level &gt;30 mg/L, max. 50 mg/L</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Serum</td>
<td>If determined</td>
<td>1.0 - 4.0 mg/L (amiodarone + desethylamiodarone)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Serum</td>
<td>If determined</td>
<td>4 - 10 mg/L</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Full blood</td>
<td>If deviant from reference</td>
<td>100 - 200 µg/L</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Plasma</td>
<td>If determined</td>
<td>0.8 - 2 µg/L</td>
</tr>
<tr>
<td>Fenobarbital</td>
<td>Serum</td>
<td>If determined</td>
<td>20 - 40 mg/L</td>
</tr>
<tr>
<td>Fenytoin</td>
<td>Serum</td>
<td>If determined</td>
<td>8 - 18 mg/L (free fenytoin: normal ± 10% of total)</td>
</tr>
<tr>
<td>Flucytosin</td>
<td>Serum</td>
<td>If determined</td>
<td>Low level &gt;25 mg/L, top level &lt;100 mg/L</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>Serum</td>
<td>If deviant from reference</td>
<td>Low level &lt;1 mg/L, top level &gt; 6 mg/L, max. 20 mg/L</td>
</tr>
<tr>
<td>Kiridine</td>
<td>Serum</td>
<td>If determined</td>
<td>2.5 - 5.0 mg/L</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Serum</td>
<td>If determined</td>
<td>1.5 - 5.0 mg/L</td>
</tr>
<tr>
<td>Lithium</td>
<td>Serum</td>
<td>If determined</td>
<td>0.8 - 1.2 mmol/L; prophylaxis 0.6 - 0.8 mmol/L; geriatric patients 0.4 - 0.8 mmol/L</td>
</tr>
<tr>
<td>Procaïnamide</td>
<td>Plasma</td>
<td>If determined</td>
<td>4 - 8 mg/L</td>
</tr>
<tr>
<td>Theofyllin</td>
<td>Serum</td>
<td>If determined</td>
<td>8 - 18 mg/L</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Serum</td>
<td>If deviant from reference</td>
<td>Low level &lt;1 mg/L, top level &gt;6 mg/L, max. 20 mg/L</td>
</tr>
<tr>
<td>Valproïnic acid</td>
<td>Serum</td>
<td>If determined</td>
<td>40 - 100 mg/L</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Serum</td>
<td>If deviant from reference</td>
<td>Low level 8 - 15 mg/L</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Serum</td>
<td>If deviant from reference</td>
<td>Low level 2.0 - 5.0 mg/L</td>
</tr>
</tbody>
</table>
Development of the surgical causality assessment method

The following methods were compared in the development of the causality assessment with expert judgement: the WHO-UMC causality assessment method\textsuperscript{34}, Naranjo probability scale\textsuperscript{25}, simplified Yale algorithm by Kramer et al.\textsuperscript{35} and causality assessment method by Arimone et al.\textsuperscript{36}. This comparison resulted in a causality assessment method primarily based on the Naranjo probability scale with defined categories based on the WHO-UMC causality assessment method (table 2). The methods developed by Kramer et al. and Arimone et al. were comparable with the content of the other methods and were therefore incorporated into the developed causality questions. To classify harm in the severity assessment, the Common Terminology Criteria Adverse Events (CTCAE) tool\textsuperscript{37} and National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) index\textsuperscript{38} were compared. The CTCAE scale provides detailed descriptions of AEs according to five categories of severity, ranging from mild to death related to the AE. The NCC MERP was originally developed to categorize errors instead of AEs. For this reason and to enhance the standardization of the assessment, the CTCAE scale was chosen to assess the severity of ADEs in the surgical population.

Reliability

Reliability of the surgical trigger tool

The reviewers detected 80, 91 and 96 triggers, respectively, with the surgical trigger tool. Substantial agreement was observed among the reviewers in detecting triggers [Fleiss kappa 0.71, 95% confidence interval (CI): 0.59–0.82, $P < 0.001$]. In addition, between the pairs of reviewers, high levels of agreement were reached, as shown in Table 3.

For the intra-rater agreement, there was an almost perfect strength of agreement within the reviewer (Cohen’s kappa 0.83, 95% CI: 0.78–0.89, $P<0.001$) on the separate occasions with a percentage of agreement of 98.5%.

Reliability of the surgical causality assessment method

The expert panels assessed 31 and 16 ADEs, respectively, in the test patients with one and more triggers. Table 4 shows that the strength of agreement between the expert panels in the causality assessment was fair, and that the intra-rater agreement of one expert panel on two separate occasions was moderate. For the preventability assessment, the expert panels found two and one preventable ADEs, respectively. The strength of agreement for the inter- and intra-rater was substantial; both showed 98.4% agreement.

The percentage of agreement between the expert panels regarding the severity of 15 ADEs was 67.0%. The percentage of agreement in the intra-rater severity assessment of 22 ADEs was 82.0%. The kappa calculation for severity was not accurate due to the low number of ADEs that received consensus and was therefore not executed.
Outcome assessment

In the surgical cohort of 262 patients, we found 538 triggers. Most scored triggers were anti-emetics >48 hours post-operative (16.7%), interdisciplinary consultation post-operative (11.7%) and ECG (10.6%). Several triggers were not found in our population (see Table 5).

We found 91 ADEs in 76 patients, of which 7.7% were scored preventable by the expert team. Most ADEs were related to gastrointestinal events (54.9%) and central nervous system events (15.4%). Of the preventable ADEs, 42.9% were related to renal function and/or electrolyte disorders. The severity of ADEs was 93.4% mild to moderate and 6.6% severe to life-threatening. However, 28.6% of the preventable ADEs were scored severe to life-threatening. ADEs were 73.6% related to medication classified in the ATC-group ‘Nervous System’, such as opioids.

Comparing our ADE trigger tool with the trigger tool from Rozich et al. 19, we specified seven triggers, and we added 33 triggers from other trigger tools20,11,15,23 and based on expert opinion. With our surgical trigger tool, we scored an additional 363 triggers in the total surgical cohort. With the added triggers, an additional 18 ADEs were found, which represents 19.8% of the total number of ADEs. Furthermore, we found three more preventable ADEs (42.9% of the total pADEs), all related to electrolyte disturbances.
Furthermore, we found three more preventable ADEs (42.9% of the total pADEs), all related to added triggers, an additional 18 ADEs were found, which represents 19.8% of the total number of ADEs.

Most ADEs were related to gastrointestinal events (54.9%) and central nervous system events (15.4%). (10.6%). Several triggers were not found in our population (see Table 5).

<table>
<thead>
<tr>
<th>TABLE 2. CAUSALITY, SEVERITY AND PREVENTABILITY ASSESSMENT METHOD FOR THE SURGICAL POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAUSALITY POTENTIAL ADE (ASSOCIATED WITH TRIGGER)</strong></td>
</tr>
<tr>
<td>1. <strong>Did the patient suffered unintentional harm during hospitalisation?</strong></td>
</tr>
<tr>
<td>Yes, namely...</td>
</tr>
<tr>
<td>2. <strong>Is there a suspected drug prescribed?</strong></td>
</tr>
<tr>
<td>Yes, namely...</td>
</tr>
<tr>
<td>3. <strong>Is such harm by this drug previously described?</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>4. <strong>When was the suspected drug prescribed for the first time?</strong></td>
</tr>
<tr>
<td>During hospitalisation</td>
</tr>
<tr>
<td>5. <strong>Did the harm appear subsequent to administration of suspected drug?</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>6. <strong>Did the harm improve after discontinuation or after administration of a specific antagonist/antidote?</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>7. <strong>Did the harm reappear when the drug was re-administered?</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>8. <strong>Did the harm worsen after increasing the dose or decreased the severity with lower doses?</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>9. <strong>Are there any similar reactions to the same or similar drugs known in the past patient history?</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>10. <strong>Are there any alternative causes other than the suspected drug that could have caused the reaction on their own?</strong></td>
</tr>
<tr>
<td>Yes, namely...</td>
</tr>
<tr>
<td>11. <strong>Was the incriminated drug detected in toxic concentrations in blood (fluids)?</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>12. <strong>Was the harm confirmed by objective evidence?</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CAUSALITY</strong></th>
<th><strong>SEVERITY</strong></th>
<th><strong>PREVENTABILITY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td>Mild</td>
<td>Certain</td>
</tr>
<tr>
<td>Probable</td>
<td>Moderate</td>
<td>Probable</td>
</tr>
<tr>
<td>Possible</td>
<td>Severe</td>
<td>Possible</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Life-threatening</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Conditional</td>
<td>Death</td>
<td>Conditional</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td></td>
<td>Unclassifiable</td>
</tr>
</tbody>
</table>
### Table 3. Inter-rater agreement on triggers between pairs of reviewers

<table>
<thead>
<tr>
<th>Agreement</th>
<th>Kappa</th>
<th>95% CI</th>
<th>p</th>
<th>Percentage of agreement (%)</th>
<th>Strength of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rater 1 – rater 2</td>
<td>0.70</td>
<td>0.62–0.77</td>
<td>&lt;0.001</td>
<td>97.8</td>
<td>Substantial</td>
</tr>
<tr>
<td>Rater 1 – rater 3</td>
<td>0.74</td>
<td>0.67–0.82</td>
<td>&lt;0.001</td>
<td>98.3</td>
<td>Substantial</td>
</tr>
<tr>
<td>Rater 2 – rater 3</td>
<td>0.69</td>
<td>0.61–0.77</td>
<td>&lt;0.001</td>
<td>98.0</td>
<td>Substantial</td>
</tr>
</tbody>
</table>

*Cohen’s kappa statistics. CI=Confidence interval.

### Table 4. Inter- and intra-rater agreement on causality and preventability among two expert panels

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Agreement</th>
<th>Kappa</th>
<th>95% CI</th>
<th>p</th>
<th>Percentage of agreement (%)</th>
<th>Strength of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causality</strong></td>
<td>Inter-rater</td>
<td>0.38</td>
<td>0.18–0.58</td>
<td>0.001</td>
<td>68.9</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>Intra-rater</td>
<td>0.41</td>
<td>0.19–0.64</td>
<td>0.001</td>
<td>70.5</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Preventability</strong></td>
<td>Inter-rater</td>
<td>0.66</td>
<td>0.38–1.00</td>
<td>&lt;0.001</td>
<td>98.4</td>
<td>Substantial</td>
</tr>
<tr>
<td></td>
<td>Intra-rater</td>
<td>0.79</td>
<td>0.47–1.00</td>
<td>&lt;0.001</td>
<td>98.4</td>
<td>Substantial</td>
</tr>
</tbody>
</table>

*Cohen’s kappa statistics. 1Percentile interval after bootstrapping, because of invalid asymptotic standard errors. CI=Confidence interval.
### Table 5. Triggers Scored in the Surgical Cohort (262 Patients)

<table>
<thead>
<tr>
<th>No.</th>
<th>Trigger</th>
<th>Scored N (%)</th>
<th>No.</th>
<th>Trigger</th>
<th>Scored N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>TOTAL</strong></td>
<td>538 (100)</td>
<td>26.</td>
<td>Request for faeces culture of <em>Clostridium difficile</em></td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>1.</td>
<td>Anaphylactic shock</td>
<td>0</td>
<td>27.</td>
<td>Hyperglycaemia (&gt;20 mmol/L)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>2.</td>
<td>Exacerbation COPD/Asthma</td>
<td>2 (0.4)</td>
<td>28.</td>
<td>Hypoglycaemia (&lt;2.8 mmol/L)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>3.</td>
<td>Hepatotoxicity</td>
<td>0</td>
<td>29.</td>
<td>Raised hepatic levels: ALP / ALT / AST 3x normal and/or Bilirubin &gt;34 umol/L</td>
<td>42 (7.8)</td>
</tr>
<tr>
<td>4.</td>
<td>All kinds of infections &gt;72h post-operative</td>
<td>39 (7.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Seizure</td>
<td>0</td>
<td>30.</td>
<td>Hyperkalemia &gt;5 mmol/L</td>
<td>21 (3.9)</td>
</tr>
<tr>
<td>6.</td>
<td>Myocardial ischemia</td>
<td>2 (0.4)</td>
<td>31.</td>
<td>Hypokalemia &lt;2.5 mmol/L</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>7.</td>
<td>Newly diagnosed peptic ulcer</td>
<td>0</td>
<td>32.</td>
<td>INR &gt;6</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>8.</td>
<td>Nefrotoxicity</td>
<td>0</td>
<td>33.</td>
<td>Creatinine &gt;100 µmol/L and more than doubled</td>
<td>11 (2.0)</td>
</tr>
<tr>
<td>9.</td>
<td>Ototoxicity</td>
<td>0</td>
<td>34.</td>
<td>Leukocytes &lt;3x10^9/L</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>10.</td>
<td>Bleeding post-operative</td>
<td>5 (0.9)</td>
<td>35.</td>
<td>Positive blood culture during use of antibiotics</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>11.</td>
<td>New rash / urticaria</td>
<td>2 (0.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Thrombo-embolic complication</td>
<td>1 (0.2)</td>
<td>36.</td>
<td>Flumazenil</td>
<td>0</td>
</tr>
<tr>
<td>13.</td>
<td><strong>EVENT</strong></td>
<td></td>
<td>37.</td>
<td>Antidiarrhoeal</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>14.</td>
<td>Abrupt medication stop with a documented AE</td>
<td>30 (5.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>Blood pressure systolic &lt; 80 mmHg</td>
<td>19 (3.5)</td>
<td>38.</td>
<td>Anti-emetics &gt;48h post-operative</td>
<td>90 (16.7)</td>
</tr>
<tr>
<td>16.</td>
<td>Blood transfusion</td>
<td>43 (8.0)</td>
<td>39.</td>
<td>Protrombin complex</td>
<td>0</td>
</tr>
<tr>
<td>17.</td>
<td>Electrocardiography post-operative</td>
<td>57 (10.6)</td>
<td>40.</td>
<td>Tranexamic acid</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>18.</td>
<td>Gastroscopy post-operative</td>
<td>13 (2.4)</td>
<td>41.</td>
<td>(Nor)epinephrine</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>19.</td>
<td>Interdisciplinary consultation post-operative</td>
<td>63 (11.7)</td>
<td>42.</td>
<td>Glucose &gt;5%</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>20.</td>
<td>Newly started anticoagulation therapy</td>
<td>5 (0.9)</td>
<td>43.</td>
<td>Vitamin K</td>
<td>0</td>
</tr>
<tr>
<td>21.</td>
<td>Death</td>
<td>2 (0.4)</td>
<td>44.</td>
<td>Desmopressin</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>22.</td>
<td>Unplanned transfer to ICU/CCU/MCU post-operative</td>
<td>6 (1.1)</td>
<td>45.</td>
<td>Naloxone</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>23.</td>
<td>Postpone operation</td>
<td>6 (1.1)</td>
<td>46.</td>
<td>Eptacog alfa, activated</td>
<td>0</td>
</tr>
<tr>
<td>24.</td>
<td>Patient fall/ lethargy/ oversedation</td>
<td>7 (1.3)</td>
<td>47.</td>
<td>Protamin</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td></td>
<td><strong>LABORATORY</strong></td>
<td></td>
<td>48.</td>
<td>Resonium® Sorbisterit®</td>
<td>0</td>
</tr>
<tr>
<td>25.</td>
<td>Abrupt Hemoglobin-drop of 25% or more &gt;24h post-operative</td>
<td>11 (2.0)</td>
<td>49.</td>
<td>Start antihistamine</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td></td>
<td>aPTT &gt;100 seconds</td>
<td>4 (0.7)</td>
<td>50.</td>
<td>Start antymycoticum</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51.</td>
<td>Medication levels</td>
<td>0</td>
</tr>
</tbody>
</table>
**Discussion**

Here, we demonstrated an effective and reproducible method for standardized assessment of ADEs in surgical patients. This method comprised a specified surgical trigger tool with 51 triggers and was combined with a standardized causality assessment method with expert judgement\(^{25,34}\). The surgical trigger tool produced reliable and reproducible results when used to detect ADEs in the medical records of surgical patients. High levels of agreement were reached among the reviewers. The assessment of medication-related harm produced an acceptable agreement. This method can be a useful alternative to existing trigger tool methods, in particular to assess medication safety in surgical patients.

We chose to assess the inter- and intra-rater agreement of the assessment method to test its reliability rather than validate our assessment method by applying complete record review on the same patient population. Complete record review is liable to subjectivity of the reviewers (information bias) and very time consuming. Ideally, a validation is performed by comparing a new tool with the gold standard. However, in ADE detection, a true gold standard is lacking. Therefore, testing the reliability and reproducibility of the surgical trigger tool is the closest possible way to meet validation and a generally accepted method\(^{23,26,27}\).

To demonstrate the additional value of our method, we retrospectively compared it with an existing method for detecting ADEs\(^{93}\). With the present tool, we found many additional triggers, ADEs and preventable ADEs compared with the Rozich's trigger tool method. This suggests that the surgical trigger tool is a good alternative for the surgical population.

In contrast to the present evaluation of the surgical trigger tool, other studies\(^{21,39}\) evaluated a trigger tool only by determining agreement for the presence of ADEs, not the detection of triggers. Naessens et al. reported comparable data on inter-rater agreement for identifying triggers to detect in-hospital AEs (kappa values ranging from 0.53 to 0.73) rather than ADEs\(^{40}\). Another study showed a kappa value of 0.62 for detecting triggers between two nurses with a paediatric trigger tool\(^{41}\). Although other outcomes were used, present reliability results were comparable with results from other studies.

A larger number of patients is needed to calculate positive predictive values of an individual trigger in relation to an ADE\(^{42}\) and to compare the positive predictive values for ADEs among related triggers. For example, a larger sample size is required to determine whether the triggers ‘hepatotoxicity’ and ‘raised hepatic levels’, both designating the same toxicity, led to different ADEs or detected more ADEs when used together. This could be an area of future research.

We found the majority of the triggers during the post-operative period on the surgical ward. Many medication changes that occur in the days after surgery are related to normal post-operative care, but the changes are also due to post-operative complications that require additional medication. That period can potentially benefit from surveillance by a clinical pharmacist. Medication event triggers during surgery and peri-operatively cannot always be directly influenced by a clinical pharmacist. However, medication given during surgery can be observed, and interventions may be needed to prevent or reduce harm before and after surgery. Therefore, triggers detectable during
operation were included, such as the administration of ‘tranexamic acid’ during surgical bleeding. In these cases, anticoagulation medication must be adjusted after surgery.

Agreement on the causality assessment between the expert panels was less favourable than agreement on the triggers. In literature, the kappa values for the causality assessment are between 0.65 and 0.98 among two or more independent reviewers. In addition, two studies have shown kappa values between 0.4 and 0.6 for the causality assessment of triggers with AEs. We assessed agreement between two different expert panels with two different experts rather than between individual experts. It is known that these types of causality assessment methods are liable to subjectivity and interaction of expert members, as these assessments are primarily based on experience. However, the present method will be used to measure changes in the ADE rates before and after intervention using the same expert panels. The causality assessment method should thus be applied consistently, and therefore, we considered our fairly reliable inter and intra-rater results for the causality assessment of ADEs (kappa values of 0.38 and 0.41, respectively) acceptable.

Notably, the expert panels did mainly agree on the preventability of ADEs. Because the intended use of the ADE assessment method is to measure avoidable medication-related harm in the surgical population, this method performs with high reliability. The agreement regarding the severity assessment was also acceptable. We did not calculate Cohen’s kappa statistic for the severity assessment because of the low number of cases (ADEs) in the test population.

Some limitations of this study must be noted. First, we did not validate our assessment method by comparing it to a gold standard or other existing methods. To compensate for this issue, we performed a retrospective comparison with our method and the ADE trigger tool by Rozich et al. as previously described. Unfortunately, data on the adapted triggers were not available, only on the added triggers to the surgical trigger tool. Second, some triggers did not appear in this population. To make this assessment method even more efficient and specific, it may need modifications in different settings. However, uncommon events, such as ototoxicity, can have a severe impact on the patient. They are therefore relevant in the trigger tool list and it is preferable to maintain the surgical trigger tool in its current form. Another important limitation of using retrospective methods to detect ADEs is information bias. A patient record analysis depends on the information documented by doctors and nurses. The underreporting of medical errors by medical care providers is likely and introduces an under-detection of ADEs. Furthermore, the amount of patient data provided to the expert panels was restricted. This was intended to standardize the assessment process. However, it may lead to the under-detection of ADEs, although the entire medical records were reviewed using the trigger tool. This is less of a problem for an instrument that measures changes in ADE occurrence than it would be for incidence studies.

This targeted trigger tool for standardized assessment of ADEs in surgical patients shows excellent agreement between reviewers. The assessment of medication-related harm had acceptable agreement. Compared with an existing ADE trigger tool method, the present method found almost 20% extra ADEs. This method can be a useful alternative to existing trigger tool methods, in particular to assess medication safety in surgical patients.
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Collaborators

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A targeted method to assess ADEs
