

DEVELOPMENT OF A STANDARDIZED CHART REVIEW METHOD TO IDENTIFY DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PEOPLE

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1 **ABSTRACT**

2 **Aim:** We aimed to develop a standardized chart review method to identify drug-related
3 hospital admissions (DRA) in older people caused by non-preventable adverse drug reactions
4 and preventable medication errors including overuse, underuse and misuse of medications: the
5 DRA adjudication guide.

6 **Methods:** The DRA adjudication guide was developed based on design and test iterations with
7 international and multidisciplinary input in 4 subsequent steps: literature review, evaluation of
8 content validity using a Delphi consensus technique, a pilot test and a reliability study.

9 **Results:** The DRA adjudication guide provides definitions, examples and step-by-step
10 instructions to measure DRA. A 3-step standardized chart review method was elaborated
11 including 1) data abstraction, 2) explicit screening with a newly developed trigger tool for DRA
12 in older people and 3) consensus adjudication for causality by a pharmacist and a physician
13 using the World Health Organization-Uppsala Monitoring Centre and Hallas criteria. A 15-
14 member international Delphi panel reached consensus agreement on 26 triggers for DRA in
15 older people. The DRA adjudication guide showed good feasibility of use and achieved
16 moderate inter-rater reliability for the evaluation of 16 cases by 4 European adjudication pairs
17 (71% agreement, kappa = 0.41). Disagreements arose mainly for cases with potential underuse.

18 **Conclusions:** The DRA adjudication guide is the first standardized chart review method to
19 identify DRA in older persons. Content validity, feasibility of use and inter-rater reliability were
20 found to be satisfactory. The method can be used as an outcome measure for interventions
21 targeted at improving quality and safety of medication use in older people.

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28 **What is already known about this subject**

- 29 • Drug-related hospital admissions represent a growing patient safety threat in older people.
30 • Identifying drug-related hospital admissions in older people is complex and there is lack of
31 a standardized approach to identify drug-related hospital admissions.

32 **What this study adds**

- 33 • We developed a standardised chart review method to measure drug-related hospital
34 admissions in older persons.
35 • Content validity, feasibility of use and inter-rater reliability were found to be satisfactory.
36 • The method can be used as an outcome measure for interventions targeted at improving
37 quality and safety of medication use in older people.

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52 INTRODUCTION

53 Adverse drug events (ADEs) are a leading cause of iatrogenic harm globally.^[1, 2] A significant
54 proportion of ADEs results in hospitalisation and these so-called drug-related hospital
55 admissions (DRA) have serious clinical and economic consequences.^[3-6] DRA can result from
56 non-preventable adverse drug reactions (ADR) or from preventable medication errors.

57 Older adults have almost a seven-fold increased risk of experiencing a DRA compared to
58 younger persons due to several risk factors such as multi-morbidity and polypharmacy.^[7]
59 Around 70% of DRA in older people are caused by potentially preventable ADEs mainly
60 resulting from poor medication adherence and inappropriate prescribing.^[8-13] The latter
61 includes the prescription or use of more drugs than are clinically needed (overuse), the
62 incorrect prescription or use of drugs that are needed (misuse) and the failure to prescribe or
63 use drugs that are needed (underuse).^[14] Identifying DRA in older people is challenging
64 because ADEs often present as common geriatric problems such as falls, confusion or renal
65 impairment which might be due to the ageing process, underlying diseases or medications.^{[13,}
66 ^{15]}

67 No standardised and validated method to identify DRA in older people exists in the literature.
68 Yet measuring DRA is potentially an important issue in the light of the World Health
69 Organisation's Global Patient Safety challenge on medication-related harm.^[2] Studies have
70 reported DRA prevalence rates ranging from 6% to 50% of all admissions in older adults.^[16-20]
71 The wide variance in prevalence rates is associated with the considerable heterogeneity in
72 definitions and methods used to identify DRA, the study population and the setting.^[20, 21] DRA
73 identification often relies on a highly subjective and variable process and few attempts have
74 been made to measure DRA resulting from underuse of medications.^[12, 19, 22, 23]

75 We aimed to develop a standardized chart review method to identify DRAs resulting from ADR,
76 overuse, misuse and underuse of medications, specific to older people: the DRA adjudication
77 guide. In this paper we present the developmental pathway of the DRA adjudication guide and
78 the evaluation of its content validity, feasibility of use and reliability, which are defined as
79 desirable attributes of a quality measure by the Agency for Healthcare Research and Quality.^[24]

80 The DRA adjudication guide will be used in 4 European centres to measure the primary
81 outcome DRA in the OPERAM trial (<http://operam-2020.eu>) that will assess the impact of a
82 pharmacotherapy optimisation intervention in 2000 multi-morbid older people.

83 **METHODS**

84 **Design**

85 The DRA adjudication guide was developed in 4 subsequent steps: (I) the first draft of the guide
86 was developed based on literature review; (II) this version was subsequently refined based on
87 evaluation of content validity by a Delphi expert panel; (III) user-feedback in a pilot test and
88 (IV) a reliability study (Figure 1).

89 **Literature review**

90 Two literature searches were performed in PubMed by the first author for articles published
91 between January 1, 1990 and August 1, 2015. Screening of titles and abstracts and data
92 extraction was performed by the first author.

93 A first exploratory search aimed to review existing structured ADE or DRA identification
94 approaches to inform the development of the overall DRA identification strategy. The search
95 included the following medical subject headings (MeSH): 'Patient admission', 'Drug-related
96 side effects and adverse reactions', 'Quality assurance, Health Care', 'Patient outcome
97 assessment'. Studies published in English, French or Dutch that focused on defining, identifying
98 and/or characterizing ADE or DRA in the adult in-hospital setting were included.

99 A second literature search aimed to review common causes for DRA in older people to inform
100 the development of a trigger tool for DRA in older people for inclusion in the DRA adjudication
101 guide. To improve efficiency and to standardize identification of ADEs, trigger-based chart
102 review has been advocated as the premier ADE identification approach.^[25-27] Triggers are
103 defined as 'occurrences, prompts or flags' found upon chart review that 'trigger' further
104 investigation to determine the presence or absence of an adverse event.^[28] Trigger tools have
105 been designed for a variety of clinical settings but to our knowledge, no trigger tool for
106 identifying DRA in older people exists. To compile a preliminary trigger tool, the second
107 literature search aimed to identify common causes for DRA in older people and to review

108 previously developed adverse event triggers tools designed for other settings. PubMed was
109 searched using the following search terms and/or combinations: 'Aged'[MeSH], 'Drug-Related
110 Side Effects and Adverse Reactions'[MeSH], 'Hospitalization'[MeSH], 'Trigger'[All fields],
111 'Adverse drug events trigger tool'[All fields], 'Pharmaceutical preparations'[MeSH],
112 'Underuse'[All fields], 'Prescribing omission'[All fields]. Studies on hospitalizations in people
113 aged ≥ 65 years resulting from preventable ADEs and non-preventable ADRs were included.
114 Studies on the development or evaluation of adverse event trigger tools designed for other
115 settings were also included. Studies on DRA in patients younger than 65 years were excluded.
116 Trigger tool studies focusing on specific patient groups such as surgical patients were also
117 excluded.

118 A data extraction form was developed to document study characteristics including study aims,
119 population, design, setting, methods used to detect ADE or DRA, causality algorithms used,
120 professionals involved in ADE or DRA assessment, most frequent causes of DRA, most frequent
121 medications involved or omitted in DRA, triggers and their positive predictive value.

122 **Evaluation of content validity**

123 Content validity refers to the relationship between an instrument's content and the construct
124 it is intended to measure.^[29] In the absence of a gold standard to measure DRA, content validity
125 of the DRA adjudication guide was assessed by an expert panel.

126 First, the overall DRA identification method suggested by the guide was agreed on a consensus
127 basis through face-to-face discussions by 3 physicians (BB, JBB, JD) and 2 clinical pharmacists
128 (AS, OD) with expertise in geriatric pharmacotherapy and medication safety.

129 Secondly, a 2-round online modified Delphi survey using LimeSurvey[®] software was conducted
130 to validate the triggers derived from the literature review. The Delphi method is a consensus
131 technique that is widely used for questions addressing medication safety in older adults.^[30] A
132 modified online 2-round Delphi survey was selected in this study as a way to combine scientific
133 rigor and pragmatism to obtain consensus from a geographically diverse expert panel. Experts
134 were selected based on their recognised academic or clinical expertise on the subject of drug-
135 related morbidity in older patients or were personal contacts. Of the 29 experts invited,

136 respectively 15 and 14 experts from 8 different countries took part in the first and second
137 Delphi round (Table 1).

138 The Delphi panel was asked to assess the content validity of the preliminary trigger tool, to
139 develop consensus on the most relevant triggers and to identify additional triggers.
140 Furthermore the panel was asked to assess 2 screening questions for non-triggered,
141 spontaneously detected events. In the first Delphi round participants were asked to rate, for
142 each of the 29 triggers derived from the literature and for the 2 screening questions the
143 'relevance to screen for a DRA in older people' on a 5-point Likert scale (ranging from
144 'absolutely irrelevant' to 'absolutely relevant'; relevance was defined as 'the degree to which
145 the item comprehensively includes the full scope of the outcome it intends to measure'). A
146 free-text field was provided for each item, allowing comments to improve the trigger design
147 or to suggest new triggers.

148 For each item, consensus measurement was based on the median Likert response and the
149 interquartile range. The following cut-off values of consensus were defined before data
150 analysis: consensus that a trigger should be retained if the median score on the 5-point Likert
151 scale was ≥ 4 and the 25th percentile ≥ 4 (i.e. $\geq 75\%$ of the experts considered the trigger as
152 'relevant' or 'absolutely relevant'); consensus that a trigger should be excluded if the median
153 score was < 3 and the 75th percentile < 3 (i.e. at least 75% of the experts considered the trigger
154 as 'irrelevant' or 'absolutely irrelevant'); no consensus for triggers that failed to meet either of
155 the latter cut-off values.

156 Triggers that were accepted or rejected unanimously after the first round were not presented
157 in the second round. In the second Delphi round, participants were asked to rate the triggers
158 for which revisions were suggested in the first round. Furthermore, participants were asked to
159 re-evaluate the equivocal triggers on the 5-point Likert scale, taking into account the groups'
160 responses. Participants were provided with a reminder of their own responses from round 1,
161 the median group rating and interquartile range and a summary of the comments made by
162 participants. Equivocal triggers that were rated equivocal again, were not included in the final
163 trigger tool (Supporting Information S1).

164 **Pilot test**

165 A pilot test was performed aimed at ensuring that the newly developed DRA adjudication guide
166 was a workable instrument and to identify points for improvement. For this purpose, the DRA
167 adjudication guide was piloted independently by a geriatrician and a pharmacist from one
168 centre (JBB, ST). For the pilot test, 15 cases from a medical record database of frail older patients
169 admitted to a teaching hospital were randomly selected by using a random number generator.
170 The reviewers' suggestions for improvement were discussed within the OPERAM research team
171 and modifications were subsequently implemented in the DRA adjudication guide.

172 **Reliability study**

173 A reliability study was conducted to assess whether the DRA adjudication guide yields
174 reproducible results when applied by different raters. Raters were OPERAM research team
175 members with clinical and/or research experience in geriatric medicine. Pairs of raters in 3
176 centres (Brussels, Cork and Utrecht) consisted of a pharmacist and physician (SM, FV, IW, AV,
177 SC, DOM) whereas in 1 centre (Bern) the pair was composed of physicians only (CF, CS). The
178 raters had no prior experience in using the DRA adjudication guide and were provided with a
179 video training tutorial (<https://www.youtube.com/watch?v=fadmO-WcCHM>).

180 For the purpose of the reliability study, each centre provided 4 cases of multi-morbid older
181 patients including the discharge and/or admission letter, laboratory values and medication
182 lists. Translation of the cases was performed by OPERAM research team members from their
183 mother tongue (Dutch, French, Swiss-German) to English. No formal back-translation process
184 was undertaken.

185 Raters were asked to first assess the cases individually and subsequently to come to a
186 consensus result on the case within the pair. The time needed to adjudicate a case was
187 recorded. A dichotomous outcome variable (DRA identified yes/no) was defined and inter-rater
188 reliability was determined by calculating percentage agreement and agreement corrected for
189 chance *between* pairs of raters from 4 European centres (Fleiss' kappa) as well as *within* each
190 pair (Cohen's kappa) for the dichotomous outcome variable. Kappa values were interpreted as
191 slight agreement if <0.20, fair agreement if 0.21–0.40, moderate agreement if 0.41–0.60,
192 substantial agreement if 0.61–0.8 and almost perfect agreement if 0.81–1.00.^[31] Next,

193 adjudication results and discrepancies were shared among all raters, who were asked for
194 feedback. The primary goal was to determine whether discrepancies were due to difficulties in
195 using the adjudication method, missed information or case interpretation.

196 **Ethics approval**

197 The ethics committee from the Cliniques universitaires Saint-Luc (Brussels, Belgium) provided
198 approval for anonymous use of the medical record database (reference number
199 B403201111806).

200 **RESULTS**

201 **Literature review and development of the DRA adjudication guide**

202 *Development of the overall DRA identification strategy*

203 Twenty-five studies on ADE or DRA identification were reviewed.^[3, 7, 12, 26, 27, 32-51] Chart review
204 by 2 or more reviewers has been considered as a gold standard in many patient safety studies
205 because of its high ADE yield and high specificity.^[32] To evaluate the relationship between drug
206 treatment and the occurrence of an adverse event, several causality assessment methods have
207 been developed. No causality assessment method is universally accepted but expert
208 judgement is the most widely used.^[47] Chart review is however often conducted in an implicit
209 and unstructured way, resulting in low inter-rater reliability.^[32] Our method selected to
210 adjudicate DRA therefore involved a structured chart review with the aid of a trigger tool to
211 improve efficiency and standardization in ADE detection.^[25] Previous research has
212 demonstrated that by restricting ADE detection to trigger tools only, whole classes of ADE can
213 be missed.^[32, 52, 53] Therefore two screening questions for non-triggered, spontaneously
214 detected events were also compiled.

215 A 3-step approach for DRA identification based on chart review was elaborated (Figure 2). The
216 3 steps include: 1) abstraction of a standardized list of data from the medical record into an
217 electronic case report form, the main source documents including the admission and discharge
218 letter, laboratory values and medication lists; 2) explicit screening for ADE(s) that are potential
219 DRA with the DRA trigger tool and screening questions for non-triggered events; 3)
220 adjudication: consensus judgement in terms of ADE causality and ADE contribution to hospital

221 admission with the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) and
222 Hallas criteria respectively.^[36, 54] Steps 2 and 3 are performed by an adjudication pair composed
223 of a pharmacist and a physician given their complementary knowledge and experience.^[55, 56]
224 Definitions, step-by-step instructions for use and examples are contained in the DRA
225 adjudication guide (Supporting Information S2).

226 *Development of the trigger tool*

227 Twenty-three studies on common causes of DRA in older people^[3, 7-10, 12, 16, 23, 38, 51, 57-69] and 12
228 trigger tools studies were reviewed.^[30, 52, 53, 70-78] Based on the information from the literature
229 and their own clinical expertise, the research team compiled a preliminary list of 29 triggers
230 and 2 screening questions for non-triggered events related to ADR, overuse, underuse or
231 misuse of medications. Key considerations for selecting the triggers were the reported positive
232 predictive value of the triggers, severity (i.e. the trigger should be severe enough to result in
233 hospital admission) and ease of detection. The triggers were divided in 3 categories including
234 diagnoses, abnormal laboratory values and 'other' triggers (e.g. antidote use). Each trigger was
235 elaborated with potential causative drugs or potential causes for drug underuse based on the
236 STOPP/START criteria version 2 and by consulting pharmacology and pharmacotherapy
237 references.^[79] Consequently, each trigger consists of a diagnosis or abnormal laboratory value
238 and a corresponding list of potential causative drugs or causes for drug underuse allowing
239 explicit chart screening for DRA.

240 **Evaluation of content validity**

241 None of the 29 triggers or screening questions were removed at the end of the first round by
242 the 15-member Delphi panel. Twenty-five triggers and 2 screening questions for non-triggered
243 events were rated 'relevant' or 'absolutely relevant' to screen for DRA in older people. Of the
244 items on which the group agreed, 10 triggers and 2 screening questions were adopted without
245 alteration in the final tool, whereas 15 triggers were revised according to the participants'
246 suggestions. Revisions included changing cut-off thresholds of laboratory values, adding or
247 removing medications associated with a trigger or adding more detail to the triggers. Four
248 triggers (theophylline level >20 µg/ml, rash, *Clostridium difficile* toxin positive stool, neutrophils
249 <1400/mm³) were rated equivocal.

250 After the second round, all 15 triggers with revisions were rated 'relevant' or 'absolutely
251 relevant'. Three out of 4 equivocal triggers from the first round were rated equivocal again and
252 these were removed from the trigger tool. The trigger 'neutrophils <1400/mm³' was now rated
253 relevant and was included in the final trigger tool (Supporting Information S1). Following last
254 refinements, the final 26-item trigger tool was created (Table 2).

255 **Pilot test**

256 The two reviewers involved in the pilot considered the trigger tool as a workable instrument
257 for screening for DRA. The same sets of triggers were identified by the two reviewers, however
258 adjudication of DRA was the part where most discrepancies arose. Based on feedback from the
259 reviewers, the following modifications were made after the pilot:

- 260 • The Naranjo algorithm and Therapeutic Failure Questionnaire ^[63, 80], which were
261 proposed as causality algorithms in the DRA adjudication guide v.1, were replaced by
262 the WHO-UMC causality criteria because they reflect clinical practice better. The WHO-
263 UMC criteria were adapted to allow causality assessment due to medication underuse
264 in line with Klopotoska et al.^[32]
- 265 • Discharge medications were added to the list of data to abstract to aid in the detection
266 of potential underuse.
- 267 • The DRA identification strategy and instructions for use were adapted to the process
268 that both reviewers considered as most practical.

269 **Reliability study**

270 Table 3 provides the level of agreement on the presence of a DRA between all centres and
271 within each pair per centre for 16 cases. The DRA adjudication guide achieved a moderate
272 inter-rater reliability score *between* adjudication pairs from 4 European centres (71%
273 agreement, Fleiss' kappa = 0.41). Agreement *within* each pair varied from fair to almost perfect
274 agreement (69%–94% agreement, Cohens' kappa = 0.33-0.86). The mean time needed to
275 assess a case individually was 23±6 minutes and the mean time needed for consensus
276 discussion was 13±5 minutes.

277 No differences in inter-rater reliability for DRA identification were observed for triggered and
278 non-triggered cases. Detailed analysis of the adjudication results showed that in the majority

279 of cases the same triggers and potential ADEs were identified but discrepancies arose mainly
280 on the level of assessment of contribution to hospital admission. Discrepancies arose for 8
281 cases with more subjective assessments including 5 triggered cases with potential underuse, 2
282 triggered cases with contributory reasons for admission (i.e. an ADE that is not the main reason
283 for admission but plays a substantial role in the admission)^[36] and 1 case with a non-triggered
284 DRA (Supporting Information S3).

285 **DISCUSSION**

286 To our knowledge the DRA adjudication guide is the first standardized instrument to identify
287 DRA in older persons caused by ADR, overuse, underuse and misuse of medications. The DRA
288 adjudication guide provides definitions, examples and step-by-step instructions to measure
289 DRA.

290 DRA identification is based on chart review with the aid of a trigger tool followed by structured
291 consensus judgement, an approach that has been used successfully in previous ADE studies.^[25]
292 The novelty of our method lies in the development of a trigger tool for DRA, specific to older
293 people and allowing explicit DRA screening. The DRA adjudication guide calls for a rigorous
294 evaluation of DRA including triggered and non-triggered events as well as non-preventable
295 ADR and preventable medication errors, which is the desired broader focus of studying DRA.^{[21,}
296 ^{32, 52, 53]} Furthermore, an adjudication pair composed of a pharmacist and a physician is a
297 recommended approach for evaluation of ADEs.^[55, 56]

298 To improve safety and quality of care, a valid and practical method to measure and understand
299 a problem is a critical approach to any patient safety threat.^[1, 81, 82] It has been acknowledged
300 that patient safety measures are often based on insufficient evidence and finding a balance
301 between scientific soundness and feasibility is a challenge.^[81] We addressed these requirements
302 by utilizing a rigorous developmental pathway based on design and test iterations combining
303 evidence from published literature with expert opinion and user-feedback from international
304 and multidisciplinary sources. Content validity, feasibility of use and inter-rater reliability were
305 found to be satisfactory.

306 Despite the development of a standardised procedure, variability in DRA determination
307 remains. Inter-rater reliability (IRR) *between* adjudication pairs in 4 European centres was
308 moderate, which is the most relevant criterion as it is the consensus judgement between the
309 pharmacist and physician that is of importance. Achieving a good IRR score for ADE
310 identification is a challenge inherent to retrospective chart review studies, with previous
311 adverse event studies reporting kappa scores varying from -0.077 to 0.66.^[19, 32, 56, 83-85] The
312 trigger tool allowed to detect the same triggers, yet discrepancies arose mainly on the level of
313 assessment of contribution to hospital admission. Expert judgement using causality criteria is
314 not devoid of individual subjective judgements.^[47] Exploring the reasons for discrepancies
315 highlighted the need for further training and standardisation of consensus procedures for more
316 subjective adjudications such as underuse. For example, 2 out of 4 centres in the present study
317 considered omission of a statin in a 90-year old patient admitted for myocardial infarction as
318 a DRA, whereas there is limited evidence of benefit of statins over the age of 80-85.^[86]

319 Our reliability study is the first one evaluating DRA by international adjudication teams, yet
320 rater pairs only came from 4 European countries. The IRR score can be considered as a
321 satisfactory result taking into account the following considerations: (i) participants were at the
322 beginning of their learning curve when IRR was evaluated; (ii) composition of adjudication
323 teams varied with regards to profession, clinical experience and experience in ADE
324 identification. It has been shown that IRR among different professions is lower, which explains
325 the almost perfect agreement score in the team that was composed of only physicians.^[56]; (iii)
326 cases were collected in 4 European hospitals and quality of information in source documents
327 such as admission and discharge letters therefore varied. Furthermore, translation of cases into
328 English was needed and was performed by research team members and not by a translation
329 agency, which might have resulted in differences in case quality. Moreover, interpretation of
330 cases and source documents from another country where guidelines and practices might vary,
331 contributes to complexity. However even if the DRA adjudication procedure is applied correctly
332 by all raters, a certain degree of disagreement is to be expected in adjudication of complex
333 multi-morbidity cases.

334 The following recommendations to optimize IRR will be implemented in the OPERAM trial: (i)
335 intensification of training and involvement of experienced clinicians in the adjudication teams,
336 (ii) close monitoring of IRR at different time-points to identify discrepancies and (iii) prompt
337 feedback and sharing of questions and experiences among teams.^[84, 87]

338 The adjudication guide has several limitations. Firstly, data are collected retrospectively and
339 hence are limited to the information available in medical charts. For assessment of underuse in
340 particular, information on patient preferences, life expectancy or adherence are often
341 undocumented in medical charts.^[81] To obtain an accurate picture, prospective identification
342 of DRA in combination of with patient, caregiver and healthcare professional interviews would
343 be desirable.^[33, 88, 89] Hindsight bias is another limitation of retrospective chart review; knowing
344 the outcome and its severity may influence the adjudication of causation.^[90] Furthermore, the
345 response rate of the experts invited to the Delphi survey was limited to 48%, nevertheless the
346 Delphi panel represented various disciplines and countries. Moreover, we did not specify an
347 age cut-off for older people in the Delphi survey, which might have influenced the outcome.
348 However in the literature review on which the preliminary list of triggers was based, we only
349 included studies of patients aged 65 years and older. We therefore believe that our trigger tool
350 is broad enough to trigger DRA in people aged 65 years and older, which corresponds to the
351 World Health Organization's age cut-off to define older people. Finally, we did not compare
352 the adjudication results from the 4 teams with a gold standard such as adjudication by an
353 expert panel.

354 The DRA adjudication guide is time-consuming for use in clinical practice and is designed for
355 research purposes. The method may be used to study incidence of DRA or drug-related
356 emergency department visits or as outcome measure for the evaluation of interventions to
357 optimize pharmacotherapy in older people.

358 The performance of the trigger tool for detecting DRA has not yet been evaluated. A future
359 study will determine the predictive validity, sensitivity and specificity of the trigger tool to
360 detect DRA in the OPERAM dataset. An electronic trigger tool with improved specificity
361 consisting of drug-disease combinations could help identify patients at risk of medication-
362 related harm in electronic patient records.^[91]

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384 **CONTRIBUTORS**

385 ST conceptualized and designed the study, performed the literature review and pilot test,
386 performed analysis and interpretation of data resulting from the validation, pilot and reliability
387 studies and drafted the DRA adjudication guide. OD and AS conceptualized and designed the
388 study, participated in the development and validation of the DRA adjudication guide and
389 performed analysis and interpretation of data resulting from the validation, pilot and reliability
390 studies. JBB participated in the development and validation of the DRA adjudication guide and

391 performed the pilot test. BB, JD and NR participated in the development and validation of the
392 DRA adjudication guide. SM, FV, IW, AV, CF, CS, SC and DOM participated in the reliability
393 study. ST drafted the initial manuscript with contributions from OD, AS, JBB, BB, SM, DOM, SC,
394 JD, CF and IW. All authors read and approved the final manuscript.

395 **CONFLICTS OF INTEREST**

396 All authors have no conflicts of interest to declare.

TABLES

Table 1: Characteristics of Delphi panellists

	Experts invited n (%)	Participation Round 1 n (%)	Participation Round 2 n (%)
Total	29 (100)	15 (52)	14 (48)
Profession, area of expertise			
Physician, geriatric medicine	10 (34)	6 (40)	6 (43)
Physician, internal medicine	8 (28)	2 (13)	2 (14)
Physician, primary care	1 (3)	-	-
Pharmacist, geriatric medicine	5 (17)	4 (27)	3 (21)
Pharmacist, medication safety	5 (17)	3 (20)	3 (21)
Country			
Belgium	5 (17)	5 (33)	4 (29)
Canada	1 (3)	1 (7)	1 (7)
Italy	1 (3)	-	-
Ireland	2 (7)	1 (7)	1 (7)
France	2 (7)	1 (7)	1 (7)
Switzerland	4 (14)	2 (13)	2 (14)
The Netherlands	6 (21)	3 (20)	3 (21)
United Kingdom	2 (7)	1 (7)	1 (7)
United States	6 (21)	1 (7)	1 (7)
Sex			
Female	15 (52)	9 (60)	8 (57)
Male	14 (48)	6 (40)	6 (43)

Table 2: Trigger tool for DRA in older persons

TRIGGER TOOL TO SCREEN FOR DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PERSONS			
Trigger on admission up to 48h of admission	Suspected causative drugs or causes for underuse		
Diagnoses			
Fall and/or fracture	<p>Use of any of the following drugs?</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Benzodiazepines <input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Antidepressants </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Sedating antihistamines <input type="checkbox"/> Opioids <input type="checkbox"/> Anticholinergic drugs^a <input type="checkbox"/> Other (<i>Please specify</i>): </td> </tr> </table>	<input type="checkbox"/> Benzodiazepines <input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Antidepressants	<input type="checkbox"/> Sedating antihistamines <input type="checkbox"/> Opioids <input type="checkbox"/> Anticholinergic drugs ^a <input type="checkbox"/> Other (<i>Please specify</i>):
	<input type="checkbox"/> Benzodiazepines <input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Antidepressants	<input type="checkbox"/> Sedating antihistamines <input type="checkbox"/> Opioids <input type="checkbox"/> Anticholinergic drugs ^a <input type="checkbox"/> Other (<i>Please specify</i>):	
	<p>Use of any drugs causing orthostatic hypotension?</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Calcium channel blockers <input type="checkbox"/> Diuretics <input type="checkbox"/> α1-receptor blockers <input type="checkbox"/> Nitrates <input type="checkbox"/> β-blockers <input type="checkbox"/> ACE-inhibitors </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Angiotensin receptor blockers <input type="checkbox"/> Direct renin inhibitors (e.g. aliskiren) <input type="checkbox"/> Anti-Parkinson drugs <input type="checkbox"/> Antidepressants (mainly tricyclic) <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Gliflozines (SGLT2-inhibitors) <input type="checkbox"/> Other (<i>Please specify</i>): </td> </tr> </table>	<input type="checkbox"/> Calcium channel blockers <input type="checkbox"/> Diuretics <input type="checkbox"/> α 1-receptor blockers <input type="checkbox"/> Nitrates <input type="checkbox"/> β -blockers <input type="checkbox"/> ACE-inhibitors	<input type="checkbox"/> Angiotensin receptor blockers <input type="checkbox"/> Direct renin inhibitors (e.g. aliskiren) <input type="checkbox"/> Anti-Parkinson drugs <input type="checkbox"/> Antidepressants (mainly tricyclic) <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Gliflozines (SGLT2-inhibitors) <input type="checkbox"/> Other (<i>Please specify</i>):
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	<p>If a fall is caused by hypoglycaemia, look for use of drugs contributing to hypoglycaemia (check trigger hypoglycaemia)</p>		
	<p>Underuse of any of the following drugs in patients with known osteoporosis and/or history of fragility fracture(s) and/or Bone Mineral Density T-scores of -2.5 or lower in multiple sites?</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Bone anti-resorptive therapy (e.g. bisphosphonates, strontium ranelate, teriparatide, denosumab) </td> </tr> </table>		<input type="checkbox"/> 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day)
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<p>Underuse of any of the following drugs in patients on corticosteroid therapy \geq 3 months?</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Bisphosphonates </td> </tr> </table>		<input type="checkbox"/> 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day)	<input type="checkbox"/> Bisphosphonates
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<p>Underuse of vitamin D in patients who are housebound and/or experiencing falls or with osteopenia with Bone Mineral Density T-score between -1 and -2.5 in multiple sites?</p>			

Confusion/delirium^b	<p>Use of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Benzodiazepines</td> <td><input type="checkbox"/> Opioids</td> </tr> <tr> <td><input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem</td> <td><input type="checkbox"/> Dopaminergic agonists</td> </tr> <tr> <td><input type="checkbox"/> Antipsychotics</td> <td><input type="checkbox"/> Digoxin</td> </tr> <tr> <td><input type="checkbox"/> Anti-epileptics</td> <td><input type="checkbox"/> Fluoroquinolones (<i>dose adjustment in renal impairment required</i>)</td> </tr> <tr> <td><input type="checkbox"/> Antihistamines (H1- and H2-receptor blockers)</td> <td><input type="checkbox"/> Acetylcholinesterase-inhibitors (new onset confusion in patients with dementia)</td> </tr> <tr> <td><input type="checkbox"/> Antidepressants</td> <td><input type="checkbox"/> Other anticholinergic drugs^a (<i>Please specify</i>):</td> </tr> </table> <hr/> <p>Abrupt discontinuation/rapid dose reduction of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Benzodiazepines</td> <td><input type="checkbox"/> Opioids</td> </tr> <tr> <td><input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem</td> <td><input type="checkbox"/> Lithium</td> </tr> <tr> <td><input type="checkbox"/> Corticosteroids</td> <td><input type="checkbox"/> Antipsychotics</td> </tr> <tr> <td><input type="checkbox"/> Dopaminergic agonists</td> <td><input type="checkbox"/> Other (<i>Please specify</i>):</td> </tr> <tr> <td><input type="checkbox"/> Antidepressants</td> <td></td> </tr> </table>	<input type="checkbox"/> Benzodiazepines	<input type="checkbox"/> Opioids	<input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem	<input type="checkbox"/> Dopaminergic agonists	<input type="checkbox"/> Antipsychotics	<input type="checkbox"/> Digoxin	<input type="checkbox"/> Anti-epileptics	<input type="checkbox"/> Fluoroquinolones (<i>dose adjustment in renal impairment required</i>)	<input type="checkbox"/> Antihistamines (H1- and H2-receptor blockers)	<input type="checkbox"/> Acetylcholinesterase-inhibitors (new onset confusion in patients with dementia)	<input type="checkbox"/> Antidepressants	<input type="checkbox"/> Other anticholinergic drugs ^a (<i>Please specify</i>):	<input type="checkbox"/> Benzodiazepines	<input type="checkbox"/> Opioids	<input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem	<input type="checkbox"/> Lithium	<input type="checkbox"/> Corticosteroids	<input type="checkbox"/> Antipsychotics	<input type="checkbox"/> Dopaminergic agonists	<input type="checkbox"/> Other (<i>Please specify</i>):	<input type="checkbox"/> Antidepressants	
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Acute renal impairment^b	<p>Use of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Non-steroidal anti-inflammatory drugs</td> <td><input type="checkbox"/> Rifampicin</td> </tr> <tr> <td><input type="checkbox"/> ACE-inhibitors</td> <td><input type="checkbox"/> Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir</td> </tr> <tr> <td><input type="checkbox"/> Angiotensin receptor blockers</td> <td><input type="checkbox"/> Lithium</td> </tr> <tr> <td><input type="checkbox"/> Diuretics</td> <td><input type="checkbox"/> Calcineurin Inhibitors (e.g. cyclosporine, tacrolimus)</td> </tr> <tr> <td><input type="checkbox"/> Sulphonamides</td> <td><input type="checkbox"/> Cisplatin</td> </tr> <tr> <td><input type="checkbox"/> Cephalosporins</td> <td><input type="checkbox"/> Radiology contrast medium</td> </tr> <tr> <td><input type="checkbox"/> Quinolones (ciprofloxacin)</td> <td><input type="checkbox"/> Amphotericin</td> </tr> <tr> <td><input type="checkbox"/> Aminoglycosides</td> <td><input type="checkbox"/> Bisphosphonates</td> </tr> <tr> <td><input type="checkbox"/> Vancomycin</td> <td><input type="checkbox"/> Other nephrotoxic drugs (<i>Please specify</i>):</td> </tr> <tr> <td><input type="checkbox"/> Pentamidine</td> <td></td> </tr> </table>	<input type="checkbox"/> Non-steroidal anti-inflammatory drugs	<input type="checkbox"/> Rifampicin	<input type="checkbox"/> ACE-inhibitors	<input type="checkbox"/> Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir	<input type="checkbox"/> Angiotensin receptor blockers	<input type="checkbox"/> Lithium	<input type="checkbox"/> Diuretics	<input type="checkbox"/> Calcineurin Inhibitors (e.g. cyclosporine, tacrolimus)	<input type="checkbox"/> Sulphonamides	<input type="checkbox"/> Cisplatin	<input type="checkbox"/> Cephalosporins	<input type="checkbox"/> Radiology contrast medium	<input type="checkbox"/> Quinolones (ciprofloxacin)	<input type="checkbox"/> Amphotericin	<input type="checkbox"/> Aminoglycosides	<input type="checkbox"/> Bisphosphonates	<input type="checkbox"/> Vancomycin	<input type="checkbox"/> Other nephrotoxic drugs (<i>Please specify</i>):	<input type="checkbox"/> Pentamidine			
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Dehydration	<p>Use of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Diuretics</td> <td><input type="checkbox"/> Any drugs causing vomiting</td> </tr> <tr> <td><input type="checkbox"/> Gliflozines (SGLT2-inhibitors)</td> <td><input type="checkbox"/> Any drugs causing diarrhoea</td> </tr> <tr> <td><input type="checkbox"/> Laxatives</td> <td><input type="checkbox"/> Other (<i>Please specify</i>):</td> </tr> </table>	<input type="checkbox"/> Diuretics	<input type="checkbox"/> Any drugs causing vomiting	<input type="checkbox"/> Gliflozines (SGLT2-inhibitors)	<input type="checkbox"/> Any drugs causing diarrhoea	<input type="checkbox"/> Laxatives	<input type="checkbox"/> Other (<i>Please specify</i>):																
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Bleeding^b	<p>Use of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Antiplatelets</td> <td><input type="checkbox"/> Low molecular weight heparins</td> </tr> <tr> <td><input type="checkbox"/> Vitamin K antagonists</td> <td><input type="checkbox"/> Selective serotonin reuptake inhibitors</td> </tr> <tr> <td><input type="checkbox"/> Direct oral anticoagulants</td> <td><input type="checkbox"/> Non-steroidal anti-inflammatory drugs</td> </tr> <tr> <td><input type="checkbox"/> Unfractionated heparin</td> <td><input type="checkbox"/> Other (<i>Please specify</i>):</td> </tr> </table> <hr/> <p><input type="checkbox"/> Underuse of proton pump inhibitors prophylaxis while - NSAIDs monotherapy (≥ 70 years old) or on concurrent NSAIDs and/or antiplatelets and/or corticosteroids - NSAIDs or antiplatelet or corticosteroids monotherapy with a history of peptic ulcer disease/gastrointestinal bleeding while on these drugs</p>	<input type="checkbox"/> Antiplatelets	<input type="checkbox"/> Low molecular weight heparins	<input type="checkbox"/> Vitamin K antagonists	<input type="checkbox"/> Selective serotonin reuptake inhibitors	<input type="checkbox"/> Direct oral anticoagulants	<input type="checkbox"/> Non-steroidal anti-inflammatory drugs	<input type="checkbox"/> Unfractionated heparin	<input type="checkbox"/> Other (<i>Please specify</i>):
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<input type="checkbox"/> Unfractionated heparin	<input type="checkbox"/> Other (<i>Please specify</i>):								
Stroke	<p>Underuse of any of the following drugs in patients with known chronic atrial fibrillation?</p> <table border="0"> <tr> <td><input type="checkbox"/> Vitamin K antagonists</td> <td></td> </tr> <tr> <td><input type="checkbox"/> Direct oral anticoagulants (except valvular atrial fibrillation)</td> <td></td> </tr> </table> <hr/> <p>Underuse of adequate antihypertensive therapy? * <i>Note</i>: Adequate antihypertensive therapy is defined according to the recommendations for older patients in the 2013 European ESH/ESC guidelines for the management of arterial hypertension.</p> <hr/> <p>Underuse of any of the following drugs in patients with history of coronary, cerebral or peripheral vascular disease?</p> <table border="0"> <tr> <td><input type="checkbox"/> Antiplatelets</td> <td><input type="checkbox"/> Statins** (unless end-of-life or > 85 years old)</td> </tr> </table> <p>** <i>Note</i>: Evidence for statin treatment above the age of 80-85 years is limited and clinical judgement should guide decisions in the very old, taking into account life expectancy, serious adverse events, possible drug interactions. Low to moderate intensity statin regimens are recommended. (low: simvastatin 10mg, pravastatin 10-20mg, fluvastatin 20-40 moderate: atorvastatin 10-20mg, Rosuvastatin 5-10mg, Simvastatin 20-40mg, pravastatin 40-80 mg, Fluvastatin 80 mg, Fluvastatin 40 mg BID)</p>	<input type="checkbox"/> Vitamin K antagonists		<input type="checkbox"/> Direct oral anticoagulants (except valvular atrial fibrillation)		<input type="checkbox"/> Antiplatelets	<input type="checkbox"/> Statins** (unless end-of-life or > 85 years old)		
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<input type="checkbox"/> Antiplatelets	<input type="checkbox"/> Statins** (unless end-of-life or > 85 years old)								
Thromboembolic event (DVT or PE)	<p>Underuse of adequate anticoagulation?</p> <table border="0"> <tr> <td><input type="checkbox"/> Unfractionated heparin</td> <td><input type="checkbox"/> Direct oral anticoagulants</td> </tr> <tr> <td><input type="checkbox"/> Low molecular weight heparins</td> <td><input type="checkbox"/> Vitamin K antagonists</td> </tr> </table>	<input type="checkbox"/> Unfractionated heparin	<input type="checkbox"/> Direct oral anticoagulants	<input type="checkbox"/> Low molecular weight heparins	<input type="checkbox"/> Vitamin K antagonists				
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(Recurrent) myocardial infarction or ischaemic disease	<p>Underuse of cardiovascular secondary prevention?</p> <table border="0"> <tr> <td><input type="checkbox"/> Antiplatelets (unless already anticoagulated)</td> <td><input type="checkbox"/> β-blocker/ACE-inhibitor or angiotensin receptor blocker /adequate anti-anginal therapy in case of ischaemic disease</td> </tr> <tr> <td><input type="checkbox"/> Statins** (unless end-of-life or > 85 years old)</td> <td></td> </tr> </table> <hr/> <p>Underuse of adequate antihypertensive therapy? *</p>	<input type="checkbox"/> Antiplatelets (unless already anticoagulated)	<input type="checkbox"/> β-blocker/ACE-inhibitor or angiotensin receptor blocker /adequate anti-anginal therapy in case of ischaemic disease	<input type="checkbox"/> Statins** (unless end-of-life or > 85 years old)					
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<input type="checkbox"/> Statins** (unless end-of-life or > 85 years old)									

Heart failure exacerbation	<p>Use of any drugs that could precipitate heart failure exacerbation?</p> <input type="checkbox"/> Non-steroidal anti-inflammatory drugs <input type="checkbox"/> Corticosteroids <input type="checkbox"/> Thiazolidinediones (glitazones) <input type="checkbox"/> Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) <input type="checkbox"/> Sodium-containing formulations (effervescent, dispersible and soluble medications) <input type="checkbox"/> Other (<i>Please specify</i>):
	<p>Underuse of any of the following drugs?</p> <input type="checkbox"/> β -blockers* <input type="checkbox"/> ACE-inhibitors* <input type="checkbox"/> Diuretics <p><i>Note: * β-blocker and ACE-inhibitors in heart failure due to left ventricular dysfunction</i></p>
COPD exacerbation	<p>Use of any drugs that could precipitate COPD exacerbation?</p> <input type="checkbox"/> Benzodiazepines with acute or chronic respiratory failure <input type="checkbox"/> Opioids <input type="checkbox"/> Other (<i>Please specify</i>):
	<p>Underuse of any of the following drugs?</p> <input type="checkbox"/> Single or dual inhaled bronchodilator therapy i.e. a β_2 agonist and/or anticholinergic bronchodilator according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) grade
Uncontrolled (non-neuropathic) pain	<p>Underuse of adequate pain treatment (according to the WHO analgesic ladder)?</p> <input type="checkbox"/> A strong opioid in moderate to severe pain if paracetamol, NSAIDs or weak opioids are not appropriate (e.g. because of insufficient pain relief) <input type="checkbox"/> Short-acting opioids for break-through pain during treatment with long acting opioids <input type="checkbox"/> Other (<i>Please specify</i>):
Gastrointestinal disorders (severe diarrhoea, vomiting)	<p>Use of any of the following drugs?</p> <input type="checkbox"/> Antibiotics <input type="checkbox"/> Laxatives <input type="checkbox"/> Selective serotonin reuptake inhibitors <input type="checkbox"/> Digoxin <input type="checkbox"/> Cholinesterase-inhibitors <input type="checkbox"/> Opioids <input type="checkbox"/> Non-steroidal anti-inflammatory drugs <input type="checkbox"/> Chemotherapy (<i>Please specify</i>): <input type="checkbox"/> Other (<i>Please specify</i>):

<p>Major constipation or faecal impaction</p>	<p>Use of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Chronic (stimulant) laxative use</td> <td><input type="checkbox"/> Aluminium antacids</td> </tr> <tr> <td><input type="checkbox"/> Opioids (look for underuse of laxatives with regular opioid use)</td> <td><input type="checkbox"/> Atypical antipsychotics</td> </tr> <tr> <td><input type="checkbox"/> Calcium antagonists (Mainly verapamil)</td> <td><input type="checkbox"/> Tricyclic antidepressants</td> </tr> <tr> <td><input type="checkbox"/> Calcium</td> <td><input type="checkbox"/> Bladder antimuscarinics</td> </tr> <tr> <td><input type="checkbox"/> Oral iron</td> <td><input type="checkbox"/> Other anticholinergic drugs^a</td> </tr> <tr> <td></td> <td><input type="checkbox"/> Other (<i>Please specify</i>):</td> </tr> </table>	<input type="checkbox"/> Chronic (stimulant) laxative use	<input type="checkbox"/> Aluminium antacids	<input type="checkbox"/> Opioids (look for underuse of laxatives with regular opioid use)	<input type="checkbox"/> Atypical antipsychotics	<input type="checkbox"/> Calcium antagonists (Mainly verapamil)	<input type="checkbox"/> Tricyclic antidepressants	<input type="checkbox"/> Calcium	<input type="checkbox"/> Bladder antimuscarinics	<input type="checkbox"/> Oral iron	<input type="checkbox"/> Other anticholinergic drugs ^a		<input type="checkbox"/> Other (<i>Please specify</i>):
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<input type="checkbox"/> Opioids (look for underuse of laxatives with regular opioid use)	<input type="checkbox"/> Atypical antipsychotics												
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	<input type="checkbox"/> Other (<i>Please specify</i>):												
<p>Laboratory values</p>													
<p>INR > 5</p>	<p>Look for evidence of bleeding (see trigger) to determine if an adverse drug event (ADE) has occurred. A raised INR in itself is not an ADE.</p>												
<p>Digoxin level > 2ng/ml</p>	<p>Look for signs or symptoms of digoxin toxicity (bradycardia, nausea, diarrhoea, confusion) to determine if a potential ADE has occurred. Not all levels above normal will result in an ADE.</p>												
<p>Hypoglycaemia (blood glucose < 4 mmol/L or 72 mg/dl)</p>	<p>Look for symptoms such as lethargy, tremor, confusion, faintness or administration of intravenous or oral glucose.</p> <p>Use of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Insulin</td> <td><input type="checkbox"/> MAO – inhibitors</td> </tr> <tr> <td><input type="checkbox"/> Oral hypoglycaemic agents (except metformin in monotherapy)</td> <td><input type="checkbox"/> β-blockers (masking symptoms of hypoglycaemia)</td> </tr> </table>	<input type="checkbox"/> Insulin	<input type="checkbox"/> MAO – inhibitors	<input type="checkbox"/> Oral hypoglycaemic agents (except metformin in monotherapy)	<input type="checkbox"/> β-blockers (masking symptoms of hypoglycaemia)								
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<p>Hyperglycaemia (blood glucose > 11 mmol/L or 198 mg/dl)</p>	<p>Use of any drugs that may cause or worsen hyperglycaemia?</p> <table border="0"> <tr> <td><input type="checkbox"/> Corticosteroids</td> <td><input type="checkbox"/> Protease-inhibitors</td> </tr> <tr> <td><input type="checkbox"/> Atypical antipsychotics (mainly olanzapine & clozapine)</td> <td><input type="checkbox"/> Calcineurin Inhibitors (cyclosporine, sirolimus, tacrolimus)</td> </tr> <tr> <td><input type="checkbox"/> Thiazide diuretics <i>less frequent</i></td> <td><input type="checkbox"/> Other (<i>Please specify</i>):</td> </tr> <tr> <td><input type="checkbox"/> β-blockers (except carvedilol and nebivolol) <i>less frequent</i></td> <td></td> </tr> </table> <p>In case hyperglycaemia is part of diabetic ketoacidosis or hyperosmolar hyperglycaemic state in a patient, review for underuse of insulin or oral hypoglycaemic agents.</p>	<input type="checkbox"/> Corticosteroids	<input type="checkbox"/> Protease-inhibitors	<input type="checkbox"/> Atypical antipsychotics (mainly olanzapine & clozapine)	<input type="checkbox"/> Calcineurin Inhibitors (cyclosporine, sirolimus, tacrolimus)	<input type="checkbox"/> Thiazide diuretics <i>less frequent</i>	<input type="checkbox"/> Other (<i>Please specify</i>):	<input type="checkbox"/> β-blockers (except carvedilol and nebivolol) <i>less frequent</i>					
<input type="checkbox"/> Corticosteroids	<input type="checkbox"/> Protease-inhibitors												
<input type="checkbox"/> Atypical antipsychotics (mainly olanzapine & clozapine)	<input type="checkbox"/> Calcineurin Inhibitors (cyclosporine, sirolimus, tacrolimus)												
<input type="checkbox"/> Thiazide diuretics <i>less frequent</i>	<input type="checkbox"/> Other (<i>Please specify</i>):												
<input type="checkbox"/> β-blockers (except carvedilol and nebivolol) <i>less frequent</i>													
<p>Hyperkalaemia (K⁺ > 5.5 mmol/L)</p>	<p>Use of any the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Intravenous or oral potassium</td> <td><input type="checkbox"/> Heparins (seldom, mainly when treated > 7days and concomitant other risk factors)</td> </tr> <tr> <td><input type="checkbox"/> Potassium-sparing diuretics</td> <td><input type="checkbox"/> Trimethoprim-sulfamethoxazole</td> </tr> <tr> <td><input type="checkbox"/> ACE-inhibitors</td> <td><input type="checkbox"/> Cyclosporine</td> </tr> <tr> <td><input type="checkbox"/> Angiotensin receptor blockers</td> <td><input type="checkbox"/> Tacrolimus</td> </tr> <tr> <td><input type="checkbox"/> Direct renin inhibitors (e.g. aliskiren)</td> <td><input type="checkbox"/> Other (<i>Please specify</i>):</td> </tr> <tr> <td><input type="checkbox"/> Non-steroidal anti-inflammatory drugs</td> <td></td> </tr> </table>	<input type="checkbox"/> Intravenous or oral potassium	<input type="checkbox"/> Heparins (seldom, mainly when treated > 7days and concomitant other risk factors)	<input type="checkbox"/> Potassium-sparing diuretics	<input type="checkbox"/> Trimethoprim-sulfamethoxazole	<input type="checkbox"/> ACE-inhibitors	<input type="checkbox"/> Cyclosporine	<input type="checkbox"/> Angiotensin receptor blockers	<input type="checkbox"/> Tacrolimus	<input type="checkbox"/> Direct renin inhibitors (e.g. aliskiren)	<input type="checkbox"/> Other (<i>Please specify</i>):	<input type="checkbox"/> Non-steroidal anti-inflammatory drugs	
<input type="checkbox"/> Intravenous or oral potassium	<input type="checkbox"/> Heparins (seldom, mainly when treated > 7days and concomitant other risk factors)												
<input type="checkbox"/> Potassium-sparing diuretics	<input type="checkbox"/> Trimethoprim-sulfamethoxazole												
<input type="checkbox"/> ACE-inhibitors	<input type="checkbox"/> Cyclosporine												
<input type="checkbox"/> Angiotensin receptor blockers	<input type="checkbox"/> Tacrolimus												
<input type="checkbox"/> Direct renin inhibitors (e.g. aliskiren)	<input type="checkbox"/> Other (<i>Please specify</i>):												
<input type="checkbox"/> Non-steroidal anti-inflammatory drugs													

<p>Hypokalaemia (K⁺ < 3 mmol/L)</p>	<p>Use of any of the following drugs?</p> <p><input type="checkbox"/> Loop diuretics</p> <p><input type="checkbox"/> Thiazide and thiazide-like diuretics</p> <p><input type="checkbox"/> Corticosteroids</p>	<p><input type="checkbox"/> Laxatives</p> <p><input type="checkbox"/> Salbutamol (IV or aerosol)</p> <p><input type="checkbox"/> Theophylline</p> <p><input type="checkbox"/> Other (<i>Please specify</i>):</p>
<p>Hyponatraemia (Na⁺ < 130 mmol/L)</p>	<p>Use of any of the following drugs?</p> <p><input type="checkbox"/> Diuretics</p> <p><input type="checkbox"/> Selective serotonin reuptake inhibitors</p> <p><input type="checkbox"/> Tricyclic antidepressants</p> <p><input type="checkbox"/> ACE-inhibitors</p>	<p><input type="checkbox"/> Angiotensin receptor blockers</p> <p><input type="checkbox"/> Carbamazepine & oxcarbazepine</p> <p><input type="checkbox"/> High dose cyclophosphamide</p> <p><input type="checkbox"/> Other (<i>Please specify</i>):</p>
<p>White blood cells < 3000 /mm³ or < 3 x 10³/μL</p>	<p>Use of any of the following drugs?</p> <p><input type="checkbox"/> Carbamazepine & oxcarbazepine</p> <p><input type="checkbox"/> Antipsychotics (mainly clozapine)</p> <p><input type="checkbox"/> Thyreostatics</p> <p><input type="checkbox"/> Ganciclovir</p> <p><input type="checkbox"/> Immunosuppressants</p>	<p><input type="checkbox"/> Chemotherapy (<i>Please specify</i>):</p> <p><input type="checkbox"/> Mirtazapine (first 6 weeks of treatment)</p> <p><input type="checkbox"/> Voriconazole</p> <p><input type="checkbox"/> Other (<i>Please specify</i>):</p>
<p>Platelet count < 50000 /mm³ or < 50 x 10³/μL</p>	<p>Use of any of the following drugs?</p> <p><input type="checkbox"/> Carbamazepine & oxcarbazepine</p> <p><input type="checkbox"/> Ganciclovir</p> <p><input type="checkbox"/> Unfractionated heparin</p> <p><input type="checkbox"/> Low molecular weight heparins</p> <p><input type="checkbox"/> Immunosuppressants</p> <p><input type="checkbox"/> Thienopyridines (mainly ticlopidine)</p>	<p><input type="checkbox"/> Quinine sulfate</p> <p><input type="checkbox"/> Sulfamides <i>Less frequent</i></p> <p><input type="checkbox"/> Chemotherapy (<i>Please specify</i>):</p> <p><input type="checkbox"/> Other (<i>Please specify</i>):</p>
<p>Neutrophils < 1400/mm³ or < 1.4 x 10³/μL</p>	<p>Use of any of the following drugs?</p> <p><input type="checkbox"/> Ganciclovir</p> <p><input type="checkbox"/> Antipsychotics (mainly clozapine)</p> <p><input type="checkbox"/> Thyreostatics</p> <p><input type="checkbox"/> Thienopyridines (mainly ticlopidine)</p>	<p><input type="checkbox"/> Chemotherapy (<i>Please specify</i>):</p> <p><input type="checkbox"/> Other (<i>Please specify</i>):</p>

Other			
Antidote use or treatments that suggest a potential ADE	<p>Use of any of the following drugs on the day of admission?</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Flumazenil in a patient on benzodiazepines <input type="checkbox"/> Naloxone in a patient on opioids <input type="checkbox"/> Phytonadione (vitamin K) in a patient on VKA <input type="checkbox"/> Protamine sulphate in a patient on heparins <input type="checkbox"/> Oral or intravenous glucose or glucagon in a patient taking hypoglycaemic drugs <input type="checkbox"/> Potassium supplements in case of hypokalaemia <input type="checkbox"/> Sodium polystyrene (Kayexalate) in case of hyperkalaemia </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> Adrenaline, antihistamines and corticosteroids (general drug allergy) <input type="checkbox"/> Acetylcysteine (paracetamol overdose) <input type="checkbox"/> Digoxin antibodies in a patient with supratherapeutic digoxin levels <input type="checkbox"/> Oral metronidazole or vancomycin in a patient who has recently been treated with an antibiotic that may cause <i>Clostridium difficile</i> associated diarrhoea </td> </tr> </table>	<input type="checkbox"/> Flumazenil in a patient on benzodiazepines <input type="checkbox"/> Naloxone in a patient on opioids <input type="checkbox"/> Phytonadione (vitamin K) in a patient on VKA <input type="checkbox"/> Protamine sulphate in a patient on heparins <input type="checkbox"/> Oral or intravenous glucose or glucagon in a patient taking hypoglycaemic drugs <input type="checkbox"/> Potassium supplements in case of hypokalaemia <input type="checkbox"/> Sodium polystyrene (Kayexalate) in case of hyperkalaemia	<input type="checkbox"/> Adrenaline, antihistamines and corticosteroids (general drug allergy) <input type="checkbox"/> Acetylcysteine (paracetamol overdose) <input type="checkbox"/> Digoxin antibodies in a patient with supratherapeutic digoxin levels <input type="checkbox"/> Oral metronidazole or vancomycin in a patient who has recently been treated with an antibiotic that may cause <i>Clostridium difficile</i> associated diarrhoea
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Mention of a (potential) ADE in the medical record	Assess causality using the WHO-UMC criteria		
Abrupt medication stop within 24h of admission	When medications are stopped or withheld as compared to medications taken at home, look for reasons why this was done. Abruptly stopping medications is a trigger requiring further investigation for cause. A sudden change in patient condition requiring adjustment of medications is often related to an ADE.		

ADE, adverse drug event; ADR, adverse drug reaction; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; FEV₁, forced expiratory volume in 1 second; ESH/ESC, European Society of Hypertension/European Society of Cardiology; INR, international normalised ratio, NSAIDs, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; VKA, Vitamin K antagonists

^aA list of medications with clinically relevant anticholinergic properties is available in the DRA adjudication guide; ^bDetailed definition of trigger available in the DRA adjudication guide

SCREENING QUESTIONS FOR NON-TRIGGERED, SPONTANEOUSLY DETECTED EVENTS

1. Could the main or contributory reason for admission be related to a drug or recent change in medications?

<input type="checkbox"/> Adverse drug reaction (non-preventable side effect, first allergic reaction) <input type="checkbox"/> Overuse of medication(s) (drug without an indication, too long duration of therapy, therapeutic duplication) <input type="checkbox"/> Inappropriate discontinuation (removal or dosage decrease) leading to physiological withdrawal signs/symptoms or return of the underlying disease signs/symptoms	<input type="checkbox"/> Wrong drug <input type="checkbox"/> Wrong dose (supratherapeutic or subtherapeutic) <input type="checkbox"/> Clinically significant drug-drug or drug-food interactions <input type="checkbox"/> Inappropriate monitoring <input type="checkbox"/> Other (e.g. drug not correctly dispensed/prepared/administered)
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2. Could the main or contributory reason for admission be related to underuse?

<input type="checkbox"/> Omission of an indicated drug <input type="checkbox"/> Too short duration of medication therapy	<input type="checkbox"/> Suspected adherence concerns
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Table 3: Inter-rater reliability for DRA presence between 4 adjudication pairs and per centre for the evaluation of 16 cases. *Respectively Fleiss' and Cohen's kappa were calculated to determine the level of agreement between the 4 adjudication pairs and within each centre.

Raters	% Agreement	Kappa*
4 adjudication pairs	71%	0.41
Centre 1 (2 physicians)	94%	0.86
Centre 2 (physician + pharmacist)	75%	0.42
Centre 3 (physician + pharmacist)	69%	0.33
Centre 4 (physician + pharmacist)	88%	0.74

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