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# BMJ Open

## Derivation of a clinical decision rule for emergency department head CT scanning in older adults who have fallen: study protocol.

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5 2 **Derivation of a clinical decision rule for emergency department head CT**  
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7 3 **scanning in older adults who have fallen: study protocol.**  
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## 34 **ABSTRACT**

### 35 **Introduction**

36 Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide.  
37 Older adults frequently present to the emergency department after falling. It can be challenging for  
38 clinicians to determine who requires brain imaging to rule out traumatic intracranial bleeding, and often  
39 head injury decision rules do not apply to older adults who fall. The goal of our study is to derive a  
40 clinical decision rule which will identify older adults who present to the emergency department after a  
41 fall who do not have clinically important intracranial bleeding.

### 43 **Methods and analysis**

44 This is a prospective cohort study enrolling patients aged 65 years or older, who present to the  
45 emergency department of 11 hospitals in Canada and the United States within 48 hours of having a fall.  
46 Patients are included if they fall on level ground, off a chair, toilet seat or out of bed. The primary  
47 outcome is the diagnosis of clinically relevant intracranial bleeding within 42 days of the index  
48 emergency department visit. An independent adjudication committee will determine the primary  
49 outcome, blinded to all other data. We are collecting data on 17 potential predictor variables. The  
50 treating physician completes a study data form at the time of initial assessment, prior to brain imaging.  
51 Data extraction is supplemented by an independently structured electronic medical record review. We  
52 will perform binary recursive partitioning using Classification and Regression Trees to derive a clinical  
53 decision rule.

### 55 **Ethics and dissemination**

56 The study has been approved by the research ethics boards governing all participating sites. We will  
57 disseminate our results by journal publication, presentation at international meetings and social media.

59 **Registration details** ClinicalTrials.gov NCT03745755

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3 63 **ARTICLE SUMMARY**

4  
5 64 **Strengths and limitations of this study**

- 6 65 • It can be challenging to determine which older adults have intracranial bleeding after a fall and  
7 there is little evidence to guide practice.  
8 66  
9 67 • This study will derive a clinical decision rule to determine which older emergency department  
10 patients who present after a fall do not require head CT imaging.  
11 68  
12 69 • Our clinical decision rule will be composed of routine clinical bedside and laboratory findings.  
13 70  
14 71 • The main threat to our study is that not all patients will have head CT imaging at their initial  
15 emergency department visit and we will not know if a patient dies of undiagnosed intracranial  
16 bleeding during 42-day follow up.  
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## 76 INTRODUCTION

77 In contrast to the younger population, the incidence of traumatic intracranial bleeding in older adults is  
78 rising<sup>1</sup> and has a worse prognosis.<sup>2,3</sup> Older adults are at higher risk of traumatic intracranial bleeding  
79 because there can be loss of the elastic integrity of the cerebral bridging veins and brain atrophy,  
80 allowing rapid movements of the brain within the cerebral spinal fluid with trauma. Older adults may be  
81 less able to withstand intracranial bleeding because of pre-existing comorbidity, frailty and  
82 polypharmacy.

83  
84 Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide,  
85 accounting for up to 80% of cases.<sup>4-8</sup> Fall-associated intracranial bleeding in older adults is increasing in  
86 incidence.<sup>9,10</sup> The mortality rate for fall-associated intracranial bleeding is 15%<sup>7,11</sup> (accounting for half of  
87 all fall-associated deaths<sup>12,13</sup>). Rather than seeing a decrease in these deaths, this mortality rate is  
88 rising.<sup>10</sup> Emergency departments (EDs) are managing an increasing number of older adults who have  
89 fallen<sup>14</sup> and ED visits for fall-related head injuries in older adults have increased year after year.<sup>9,13,15-17</sup>  
90 There is a paucity of evidence to guide neuroimaging for intracranial bleeding in older adults.

91  
92 The Canadian CT Head Rule can determine the need for head computed tomography (CT) in head-  
93 injured patients who experienced loss of consciousness, disorientation or amnesia after their injury.<sup>18</sup>  
94 However, older ED patients who present after a fall cannot always give a history of what happened, falls  
95 are frequently unwitnessed and many older adults who fall do not sustain a head injury. Ordering a head  
96 CT scan on every older adult who has fallen would be an inefficient and costly way to diagnose  
97 intracranial bleeding when only approximately 5% have intracranial bleeding.<sup>19</sup> Patients awaiting a CT  
98 scan will typically occupy an ED bed. CT overuse in this population not only causes prolonged ED visits,  
99 but it also contributes to ED overcrowding, which may result in worse outcomes for other patients.<sup>20</sup>  
100 Older adults are at greater risk of developing delirium the longer they stay in the ED.<sup>21</sup> There is a need  
101 for a simple bedside tool which can rapidly stratify the risk of intracranial bleeding in older ED patients  
102 who present after falling. Our aim is to derive a clinical decision rule which will identify older adults who  
103 present to the ED after a fall who do not have clinically important intracranial bleeding and therefore do  
104 not require a head CT.

105



## 106 **METHODS AND ANALYSIS**

### 107 **Study design**

108 This is a prospective cohort study designed to develop a unique clinical decision rule for ED physicians  
109 evaluating older adults who have fallen. Clinical decision rules are a commonly applied method of  
110 standardized clinical diagnostic decision-making in the ED. The rules incorporate the standardized  
111 collection and interpretation of multiple predictor variables from the patient's history, physical  
112 examination and test results to optimize evidence-based clinical decision-making. For example, clinical  
113 decision rules are used to determine which patients should have cervical spine imaging in trauma,<sup>22</sup>  
114 thoracic imaging for pulmonary embolism<sup>23</sup> and admission after syncope.<sup>24</sup> Our study follows the  
115 methodological standards for clinical decision rules in emergency medicine.<sup>25</sup>

### 117 **Patient and public involvement**

118 Prior to the protocol development, we conducted a qualitative study with older adults who were waiting  
119 in the ED for head CT after a fall. We found that diagnosing intracranial bleeding was important to the  
120 participants, that they valued testing tailored to their personal risk and shorter ED visits. This protocol  
121 was designed with feedback and input from our patient partners.

### 123 **Study population**

124 This study is conducted at 11 hospitals in Canada and the United States and enrolls patients aged 65  
125 years or older who present to the ED within 48 hours of having a fall. Patients are eligible if they fall on  
126 level ground (either inside or outside), off a chair or toilet seat or out of bed. Patients are included  
127 regardless of whether they hit their head. Patients are excluded if they fell down steps, fell from a  
128 height, were knocked down by a car/bike/pedestrian or other mechanism of injury. Patients who live  
129 outside of the hospital catchment area, who have previously been enrolled in this study, who are  
130 transferred from another hospital and who leave the ED prior to completion of their medical assessment  
131 are also excluded. Recruitment commenced on January 30, 2019. Patients are recruited 24 hours a day,  
132 seven days a week.

### 134 **Patient assessment**

135 Each patient is assessed at their index ED visit by an emergency physician who decides on the need for  
136 head CT based on clinical history and examination. It would be impractical to perform a head CT on all  
137 older adults who have fallen, for example, after a simple trip, because there is not always an indication

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3 138 for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if  
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5 139 participants return to the ED within 42 days of enrolment with new confusion, headache, loss of  
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7 140 balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological  
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9 141 symptoms, they will undergo head CT.

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### 11 143 **Outcome definition and measurement**

12  
13 144 The primary outcome is '***clinically important intracranial bleeding***' diagnosed within 42 days of the  
14  
15 145 index ED presentation. Our definition was derived after surveying specialists (including neurosurgeons,  
16  
17 146 neurologists, trauma physicians, geriatricians, thrombosis and emergency physicians) who determined  
18  
19 147 that symptoms from intracranial bleeding might develop as late as six weeks after a fall. 'Clinically  
20  
21 148 important intracranial bleeding' is defined as bleeding within the cranial vault (including subdural,  
22  
23 149 intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires  
24  
25 150 medical or surgical treatment. Medical treatment is defined as any of the following: temporary or  
26  
27 151 permanent discontinuation of anticoagulant or antiplatelet medication; administration of an  
28  
29 152 antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation.  
30  
31 153 Clinically important intracranial bleeding will be determined by independent adjudication of head CT  
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33 154 scans by the centralized outcome adjudication committee consisting of a study neurologist,  
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35 155 neurosurgeon, trauma surgeon and radiologist. The adjudicators will be blinded to all ED baseline data.  
36  
37 156 Secondary outcomes relate to the 'severity' of the intracranial bleeding: 1) neurosurgical intervention; 2)  
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39 157 intensive care admission; 3) hospital length of stay; 4) in-hospital death as determined by medical record  
40  
41 158 review.

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44 160 We found poor sensitivity (37%, 95% confidence interval: 21 to 56%) for patient-reported diagnosis of  
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46 161 intracranial bleeding.<sup>26</sup> Furthermore, our experience of personal follow up in this population<sup>27</sup> is that it is  
47  
48 162 frequently not feasible because of residence in nursing homes or baseline cognitive impairment.  
49  
50 163 Therefore, the current study follow up is restricted to systematic medical record review with  
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52 164 independent validation and enrollment is restricted to patients who reside within the hospital  
53  
54 165 catchment area.

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### 56 167 **Predictor variables**

57  
58 168 Demographic and predictor variables are collected in two ways: 1) the treating physician completes a  
59  
60 169 standardized data collection form at the time of initial patient assessment, and before the results of the

170 head CT are available (therefore blinded to outcome); 2) data is collected by trained on-site research  
 171 assistants using standardized medical record review protocols, following detailed data definitions and  
 172 instructions for systematic medical record review. We follow standardized validation procedures for all  
 173 medical record review data points: de-identified source documentation is uploaded for validation by the  
 174 coordinating centre. A query is sent to the site research assistant to resolve each discrepancy. The study  
 175 site investigator resolves discrepancies which persist after research assistant review. Table 1 details the  
 176 demographic and predictor variables collected.

**Table 1: Description of collected demographic and predictor variables**

|   | Data collected by<br>treating physician at<br>initial assessment | Data collected by<br>systematic medical<br>record review by<br>research assistant |
|---|--|---|
| <b>Predictor variables</b>                    |  |   |
| Age   |  | x   |
| Sex   |  | x   |
| Head injury (as reported by patient or carer) | x  |   |
| Loss of consciousness                         | x  |   |
| New amnesia about events of fall              | x  |   |
| History of previous major bleed <sup>28</sup> |  | x   |
| Cirrhosis                                     |  | x   |
| Previous diagnosis of ischemic stroke         |  | x   |
| Chronic renal impairment                      | x  | x   |
| Reduced Glasgow Comma Score from normal       | x  |   |
| Bruise or laceration on the head              | x  |   |
| New abnormality on neurological examination   | x  |   |
| Haemoglobin                                   |  | x   |
| Platelet count                                |  | x   |
| Anticoagulation medication                    | x  | x   |
| Antiplatelet medication                       | x  | x   |
| Clinical Frailty Score <sup>29</sup>          | x  |   |

| Descriptive variables                      |   |   |
|--|---|---|
| Living circumstances                       |   | x |
| Diabetes                                   |   | x |
| Hypertension                               |   | x |
| Active cancer within past 2 years          |   | x |
| Dementia                                   |   | x |
| History of frequent falls                  |   | x |
| Congestive heart failure                   |   | x |
| Mechanism of injury                        |   | x |
| Weight                                     |   | x |
| GCS at time of physician assessment        | x |   |
| Vomiting (once / more than once)           | x |   |
| Signs of basal skull fracture              | x |   |
| Suspected open or depressed skull fracture | x |   |
| Retrograde amnesia for >30 minutes         | x |   |
| Creatinine                                 |   | x |
| International normalized ratio (INR)       |   | x |

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We initially identified potential predictor variables by a systematic review of prior evidence. We then assessed the frequency among our population and the association between predictor and intracranial bleeding in a study of 1753 older ED patients who had fallen.<sup>27</sup> We selected 17 candidate predictor variables, which are considered to be biologically plausible and related to the outcome of intracranial bleeding, and are routinely collected in the ED: age; sex; head injury; loss of consciousness; amnesia; history of previous major bleed (International Society of Thrombosis and Haemostasis criteria<sup>28</sup>); cirrhosis; prior ischemic stroke; chronic renal impairment; GCS reduced from baseline; bruise or laceration on the head; abnormal neurological examination; haemoglobin, platelet count; anticoagulant therapy; antiplatelet therapy; and, Clinical Frailty Score.<sup>29</sup> We did not include potential predictors such as suspected open or depressed skull fractures or retrograde amnesia because these features were extremely rare among our prior study.<sup>27</sup>

## 192 **Analysis**

193 Variables with large amounts of missing data will be excluded from the models as they would be missing  
194 in clinical practice. Likewise, continuous variables whose distributions are too narrow will also be  
195 excluded. We will perform binary recursive partitioning using Classification and Regression Trees to  
196 develop a decision rule. A clinical decision rule for a life-threatening event like intracranial bleeding  
197 requires very high sensitivity. The model with a sensitivity of > 99% and the highest specificity will be  
198 selected. We will assess the derived decision rule by comparing the classification of each patient with his  
199 or her actual status for the primary outcomes. In addition, 1000 bootstrap iterations will be performed  
200 to assess the internal classification performance and overfitting of the selected decision rule.

201  
202 We will also develop a predictive risk model using multivariable logistic regression. Continuous variables  
203 may be transformed and will be fit using restricted cubic splines to relax the linearity assumption. First, a  
204 full model with all variables will be fit. To further reduce the model, backward selection without model  
205 re-fitting with  $p < 0.5$ , which has shown to have valid inference will be performed.<sup>30,31</sup> Clinically and  
206 biologically plausible interactions will be tested within the model. Internal validation to obtain unbiased  
207 and optimism corrected estimation of model performance will be done using 1000 bootstrap samples.  
208 Model discrimination will be reported using the C-statistic and a calibration plot of observed versus  
209 predicted probabilities.

## 211 **Sample size**

212 The current guidelines suggest that we would require at least 10 events per included variable.<sup>32,33</sup> We  
213 expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,<sup>19</sup> and we  
214 assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample  
215 size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).

## 217 **Sources of bias**

218 Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is  
219 collected before the primary outcome data is collected. However, it is possible that we do not identify  
220 every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of  
221 patients had a head CT during the index ED visit.<sup>27</sup> Although patients are advised to return if they  
222 develop neurological symptoms, it is possible that a patient may die of an intracranial bleed before  
223 being diagnosed. Furthermore, 42-day follow-up involves institutional electronic medical record review.

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3 224 If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial  
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5 225 bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study  
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7 226 enrollment to patients who reside within the hospital catchment area and most sites have access to  
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9 227 records from regional neurosurgical centres. In our prior study where we performed in-person follow  
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11 228 up, no patient was diagnosed with an intracranial bleed at another hospital.  
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### 230 **Study oversight**

15 231 The coordinating centre is McMaster University. Electronic data and de-identified source documents are  
16  
17 232 uploaded to a Research Electronic Data Capture (REDCap) database<sup>34,35</sup> and stored on a secure server at  
18  
19 233 McMaster University. The coordinating centre validates all data and supervises the adjudication  
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21 234 committee activities. The study steering committee consists of the site investigators.  
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### 236 **Ethics and dissemination**

25 237 Research ethics approval has been obtained from each enrolling site local research ethics board. In our  
26  
27 238 previous study on the same population,<sup>27</sup> we obtained patient consent. An interim analysis showed a  
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29 239 number of patients were confused (144/890, 16%) or died before a researcher could ask for their  
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31 240 consent (39/890, 4%). Family were often not available in the ED. In all, we were unable to obtain  
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33 241 consent from 204/890 (23%) patients. To address this problem, we obtained research ethics board  
34  
35 242 approval to include patients who were unable to give informed consent. It is essential we include  
36  
37 243 patients who cannot consent since they are often the most frail patients who are challenging to evaluate  
38  
39 244 in the ED and frequently excluded from studies. Excluding these patients could limit the generalizability  
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41 245 of our clinical decision rule. The current study has research ethics approval at all sites to include patients  
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43 246 without obtaining informed consent.  
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247

45 248 The study results will be submitted for publication in a peer reviewed journal and presented at national  
46  
47 249 and international emergency medicine meetings.  
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3 251 **AUTHORS' CONTRIBUTIONS**

4 252 The study was conceived by KdW, MM, CK, SS and AW. The protocol was designed with input from  
5 253 all authors and has been endorsed by the Network of Canadian Emergency Researchers. The study is  
6 254 being conducted by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study  
7 255 adjudicators. SP will oversee the analysis.  
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## 278 REFERENCES

- 279
- 280 1. Van den Brand CL, Karger LB, Nijman ST, Hunink MG, Patka P, Jellema K. Traumatic brain injury  
281 in the Netherlands, trends in emergency department visits, hospitalization and mortality  
282 between 1998 and 2012. *Eur J Emerg Med.* 2017;06:06.
- 283 2. Haring RS, Narang K, Canner JK, et al. Traumatic brain injury in the elderly: morbidity and  
284 mortality trends and risk factors. *J Surg Res.* 2015;195(1):1-9.
- 285 3. McIntyre A, Mehta S, Aubut J, Dijkers M, Teasell RW. Mortality among older adults after a  
286 traumatic brain injury: A meta-analysis. *Brain Injury.* 2013;27(1):31-40.
- 287 4. Chan V, Colantonio A, Chen A, Zagorski B, Parsons D, Vander Laan R. A population based  
288 perspective of acquired brain injury in older adults: How do they happen? *Brain Injury.* 2012;26  
289 (4-5):548-549.
- 290 5. Kerr ZY, Harmon KJ, Marshall SW, Proescholdbell SK, Waller AE. The epidemiology of traumatic  
291 brain injuries treated in emergency departments in North Carolina, 2010-2011. *N C Med J.*  
292 2014;75(1):8-14.
- 293 6. Albrecht JS, Hirshon JM, McCunn M, et al. Increased rates of mild traumatic brain injury among  
294 older adults in US Emergency Departments, 2009-2010. *Journal of Head Trauma Rehabilitation.*  
295 2016;31(5):E1-E7.
- 296 7. Fu WW, Fu TS, Jing R, McFaul SR, Cusimano MD. Predictors of falls and mortality among elderly  
297 adults with traumatic brain injury: A nationwide, population-based study. *PLoS ONE.* 2017;12 (4)  
298 (no pagination)(e0175868).
- 299 8. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe.  
300 *Acta Neurochirurgica.* 2015;157(10):1683-1696.
- 301 9. Hastings DL, Brieding M, Lee R. Falls and traumatic brain injuries in older adults: A worsening  
302 trend. *Journal of the American Geriatrics Society.* 2017;65:S8.
- 303 10. Sung KC, Liang FW, Cheng TJ, Lu TH, Kawachi I. Trends in Unintentional Fall-Related Traumatic  
304 Brain Injury Death Rates in Older Adults in the United States, 1980-2010: A Joinpoint Analysis. *J*  
305 *Neurotrauma.* 2015;32(14):1078-1082.
- 306 11. Fletcher AE, Khalid S, Mallonee S. The epidemiology of severe traumatic brain injury among  
307 persons 65 years of age and older in Oklahoma, 1992-2003. *Brain Injury.* 2007;21(7):691-699.
- 308 12. Chisholm KM, Harruff RC. Elderly deaths due to ground-level falls. *The American journal of*  
309 *forensic medicine and pathology.* 2010;31(4):350-354.



- 1  
2  
3 310 13. Brazinova A, Mauritz W, Majdan M, Rehorcikova V, Leitgeb J. Fatal traumatic brain injury in  
4 311 older adults in Austria 1980-2012: an analysis of 33 years. *Age Ageing*. 2015;44(3):502-506.  
5 312 14. Shankar KN, Liu SW, Ganz DA. Trends and Characteristics of Emergency Department Visits for  
6 313 Fall-Related Injuries in Older Adults, 2003–2010. *Western Journal of Emergency Medicine*.  
7 314 2017;18(5):785-793.  
8 315 15. Hartholt KA, Van Lieshout EM, Polinder S, Panneman MJ, Van der Cammen TJ, Patka P. Rapid  
9 316 increase in hospitalizations resulting from fall-related traumatic head injury in older adults in  
10 317 The Netherlands 1986-2008. *J Neurotrauma*. 2011;28(5):739-744.  
11 318 16. Korhonen N, Niemi S, Parkkari J, Sievanen H, Kannus P. Incidence of fall-related traumatic brain  
12 319 injuries among older Finnish adults between 1970 and 2011. *Jama*. 2013;309(18):1891-1892.  
13 320 17. Verma SK, Willetts JL, Corns HL, Marucci-Wellman HR, Lombardi DA, Courtney TK. Falls and fall-  
14 321 related injuries among community-dwelling adults in the United States. *PLoS ONE*. 2016;11 (3)  
15 322 (no pagination)(e0150939).  
16 323 18. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor  
17 324 head injury. *The Lancet*. 2001;357(9266):1391-1396.  
18 325 19. de Wit K, Merali Z, Kagoma YK, Mercier É. Incidence of intracranial bleeding in seniors  
19 326 presenting to the emergency department after a fall: A systematic review. *Injury*.  
20 327 2020;51(2):157-163.  
21 328 20. Kelen G, Peterson S, Pronovost P. In the Name of Patient Safety, Lets Burden the Emergency  
22 329 Department More. *Annals of Emergency Medicine*. 67(6):737-740.  
23 330 21. Émond M, Grenier D, Morin J, et al. Emergency Department Stay Associated Delirium in Older  
24 331 Patients. *Canadian Geriatrics Journal*. 2017;20(1):10-14.  
25 332 22. Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-spine rule for radiography in alert and  
26 333 stable trauma patients. *Jama*. 2001;286(15):1841-1848.  
27 334 23. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without  
28 335 diagnostic imaging: management of patients with suspected pulmonary embolism presenting to  
29 336 the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med*.  
30 337 2001;135(2):98-107.  
31 338 24. Thiruganasambandamoorthy V, Stiell IG, Sivilotti MLA, et al. Risk stratification of adult  
32 339 emergency department syncope patients to predict short-term serious outcomes after discharge  
33 340 (RiSEDS) study. *BMC Emergency Medicine*. 2014;14:8-8.

- 1  
2  
3 341 25. Stiehl IG, Wells GA. Methodologic standards for the development of clinical decision rules in  
4 342 emergency medicine. *Annals of Emergency Medicine*. 1999;33(4):437-447.  
5  
6 343 26. Selvanayagam N, Soomro A, Varner C, McLeod S, Clayton N, de Wit K. LO59: Reliability of patient  
7 344 reported exposure and outcome data in a prospective cohort study of older adults presenting to  
8 345 the emergency department. *CJEM*. 2020;22(S1):S29-S29.  
9  
10 346 27. de Wit K, Parpia S, Varner C, et al. Clinical Predictors of Intracranial Bleeding in Older Adults  
11 347 Who Have Fallen: A Cohort Study. *Journal of the American Geriatrics Society*. 2020;68(5):970-  
12 348 976.  
13  
14 349 28. Schulman S, Kearon C, the SOCOAOTS, Standardization Committee Of The International Society  
15 350 On T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic  
16 351 medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis*.  
17 352 2005;3(4):692-694.  
18  
19 353 29. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly  
20 354 people. *Canadian Medical Association Journal*. 2005;173(5):489-495.  
21  
22 355 30. Lawless JF, Singhal K. Efficient Screening of Nonnormal Regression Models. *Biometrics*.  
23 356 1978;34(2):318-327.  
24  
25 357 31. Harrell F. *Regression Modeling Strategies With Applications to Linear Models, Logistic*  
26 358 *Regression, and Survival Analysis*. Springer New York; 2001.  
27  
28 359 32. Mallett S, Royston P, Dutton S, Waters R, Altman DG. Reporting methods in studies developing  
29 360 prognostic models in cancer: a review. *BMC Medicine*. 2010;8:20.  
30  
31 361 33. Pavlou M, Ambler G, Seaman SR, et al. How to develop a more accurate risk prediction model  
32 362 when there are few events. *BMJ (Clinical research ed)*. 2015;351:h3868.  
33  
34 363 34. PA Harris, R Taylor, R Thielke, J Payne, N Gonzalez, JG. Conde, Research electronic data capture  
35 364 (REDCap). A metadata-driven methodology and workflow process for providing translational  
36 365 research informatics support, *Journal of Biomedical Informatics*. 2009;42(2):377-81.  
37  
38 366 35. PA Harris, R Taylor, BL Minor, V Elliott, M Fernandez, L O'Neal, L McLeod, G Delacqua, F  
39 367 Delacqua, J Kirby, SN Duda, REDCap Consortium, The REDCap consortium: Building an  
40 368 international community of software partners, *Journal of Biomedical Informatics*. 2019,  
41 369 May [doi: 10.1016/j.jbi.2019.103208].  
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# BMJ Open

## Which older emergency patients are at risk of intracranial bleeding after a fall? A protocol to derive a clinical decision rule for the emergency department.

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## **Which older emergency patients are at risk of intracranial bleeding after a fall?**

### **A protocol to derive a clinical decision rule for the emergency department.**

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3 34 **ABSTRACT**

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5 35 **Introduction**

6 36 Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide.  
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8 37 Older adults frequently present to the emergency department after falling. It can be challenging for  
9  
10 38 clinicians to determine who requires brain imaging to rule out traumatic intracranial bleeding, and often  
11  
12 39 head injury decision rules do not apply to older adults who fall. The goal of our study is to derive a  
13  
14 40 clinical decision rule which will identify older adults who present to the emergency department after a  
15  
16 41 fall who do not have clinically important intracranial bleeding.  
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18 42  
19 43 **Methods and analysis**

20 44 This is a prospective cohort study enrolling patients aged 65 years or older, who present to the  
21  
22 45 emergency department of 11 hospitals in Canada and the United States within 48 hours of having a fall.  
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24 46 Patients are included if they fall on level ground, off a chair, toilet seat or out of bed. The primary  
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26 47 outcome is the diagnosis of clinically relevant intracranial bleeding within 42 days of the index  
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28 48 emergency department visit. An independent adjudication committee will determine the primary  
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30 49 outcome, blinded to all other data. We are collecting data on 17 potential predictor variables. The  
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32 50 treating physician completes a study data form at the time of initial assessment, prior to brain imaging.  
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34 51 Data extraction is supplemented by an independent, structured electronic medical record review. We  
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36 52 will perform binary recursive partitioning using Classification and Regression Trees to derive a clinical  
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38 53 decision rule.  
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41 55 **Ethics and dissemination**

42 56 The study was initially approved by Hamilton Integrated Research Ethics Committee and subsequently  
43  
44 57 approved by the research ethics boards governing all participating sites. We will disseminate our results  
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46 58 by journal publication, presentation at international meetings and social media.  
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49 60 **Registration details** ClinicalTrials.gov NCT03745755  
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3 64 **ARTICLE SUMMARY**  
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5 65 **Strengths and limitations of this study**

- 6 66
- 7 67 • This cohort study aims to derive a clinical decision rule which identifies older adults at risk of intracranial bleeding after a fall.
  - 8 68 • This is a large study enrolling patients from 11 hospitals in two countries.
  - 9 69 • Potential predictor variables are recorded by emergency physicians prior to CT scanning.
  - 10 70 • The primary outcome, clinically important intracranial bleeding, is determined by an independent adjudication committee.
  - 11 71
  - 12 72 • The main limitation is that not all patients will have head CT imaging at their initial emergency department visit.
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## 77 INTRODUCTION

78 In contrast to the younger population, the incidence of traumatic intracranial bleeding in older adults is  
79 rising<sup>1</sup> and has a worse prognosis.<sup>2,3</sup> Older adults are at higher risk of traumatic intracranial bleeding  
80 because there can be loss of the elastic integrity of the cerebral bridging veins and brain atrophy,  
81 allowing rapid movements of the brain within the cerebral spinal fluid with trauma. Older adults may be  
82 less able to withstand intracranial bleeding because of pre-existing comorbidity, frailty and  
83 polypharmacy.

84  
85 Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide,  
86 accounting for up to 80% of cases.<sup>4-8</sup> Fall-associated intracranial bleeding in older adults is increasing in  
87 incidence.<sup>9,10</sup> The mortality rate for fall-associated intracranial bleeding is 15%<sup>7,11</sup> (accounting for half of  
88 all fall-associated deaths<sup>12,13</sup>). Rather than seeing a decrease in these deaths, this mortality rate is  
89 rising.<sup>10</sup> Emergency departments (EDs) are managing an increasing number of older adults who have  
90 fallen<sup>14</sup> and ED visits for fall-related head injuries in older adults have increased year after year.<sup>9,13,15-17</sup>  
91 There is a paucity of evidence to guide neuroimaging for intracranial bleeding in older adults.

92  
93 The Canadian CT Head Rule can determine the need for head computed tomography (CT) in head-  
94 injured patients who experienced loss of consciousness, disorientation or amnesia after their injury.<sup>18</sup>  
95 However, older ED patients who present after a fall cannot always give a history of what happened, falls  
96 are frequently unwitnessed and many older adults who fall do not sustain a head injury. Ordering a head  
97 CT scan on every older adult who has fallen would be an inefficient and costly way to diagnose  
98 intracranial bleeding when only approximately 5% have intracranial bleeding.<sup>19</sup> Patients awaiting a CT  
99 scan will typically occupy an ED bed. CT overuse in this population not only causes prolonged ED visits,  
100 but it also contributes to ED overcrowding, which may result in worse outcomes for other patients.<sup>20</sup>  
101 Older adults are at greater risk of developing delirium the longer they stay in the ED.<sup>21</sup> There is a need  
102 for a simple bedside tool which can rapidly stratify the risk of intracranial bleeding in older ED patients  
103 who present after falling. Our aim is to derive a clinical decision rule which will identify older adults who  
104 present to the ED after a fall who do not have clinically important intracranial bleeding and therefore do  
105 not require a head CT.

106

## 107 **METHODS AND ANALYSIS**

### 108 **Study design**

109 This is a prospective cohort study designed to develop a unique clinical decision rule for ED physicians  
110 evaluating older adults who have fallen. Clinical decision rules are a commonly applied method of  
111 standardized clinical diagnostic decision-making in the ED. The rules incorporate the standardized  
112 collection and interpretation of multiple predictor variables from the patient's history, physical  
113 examination and test results to optimize evidence-based clinical decision-making. For example, clinical  
114 decision rules are used to determine which patients should have cervical spine imaging in trauma,<sup>22</sup>  
115 thoracic imaging for pulmonary embolism<sup>23</sup> and admission after syncope.<sup>24</sup> Our study follows the  
116 methodological standards for clinical decision rules in emergency medicine<sup>25</sup> and the Transparent  
117 reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.<sup>26</sup>

### 119 **Patient and public involvement**

120 Prior to the protocol development, we conducted a qualitative study with older adults who were waiting  
121 in the ED for head CT after a fall. We found that diagnosing intracranial bleeding was important to the  
122 participants, that they valued testing tailored to their personal risk and shorter ED visits. This protocol  
123 was designed with feedback and input from our patient partners.

### 125 **Study population**

126 This study is conducted at 11 hospitals in Canada and the United States and enrolls patients aged 65  
127 years or older who present to the ED within 48 hours of having a fall. Patients are eligible if they fall on  
128 level ground (either inside or outside), off a chair, toilet seat or out of bed. Patients are included  
129 regardless of whether they hit their head. Patients are excluded if they fell down steps, fell from a  
130 height, were knocked down by a car/bike/pedestrian or other mechanism of injury. Patients who live  
131 outside of the hospital catchment area, who have previously been enrolled in this study, who are  
132 transferred from another hospital and who leave the ED prior to completion of their medical assessment  
133 are also excluded. Recruitment commenced on January 30, 2019. Patients are recruited 24 hours a day,  
134 seven days a week.

### 136 **Patient assessment**

137 Each patient is assessed at their index ED visit by an emergency physician who decides on the need for  
138 head CT based on clinical history and examination. It would be impractical to perform a head CT on all

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3 139 older adults who have fallen, for example, after a simple trip, because there is not always an indication  
4 140 for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if  
5 141 participants return to the ED within 42 days of enrolment with new confusion, headache, loss of  
6 142 balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological  
7 143 symptoms, they will undergo head CT.  
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### 145 **Outcome definition and measurement**

146 The primary outcome is '***clinically important intracranial bleeding***' diagnosed within 42 days of the  
147 index ED presentation. Our definition was derived after surveying specialists (including neurosurgeons,  
148 neurologists, trauma physicians, geriatricians, thrombosis and emergency physicians) who determined  
149 that symptoms from intracranial bleeding might develop as late as six weeks after a fall. 'Clinically  
150 important intracranial bleeding' is defined as bleeding within the cranial vault (including subdural,  
151 intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires  
152 medical or surgical treatment. Medical treatment is defined as any of the following: temporary or  
153 permanent discontinuation of anticoagulant or antiplatelet medication; administration of an  
154 antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation.  
155 Clinically important intracranial bleeding will be determined by independent adjudication of head CT  
156 scans by the centralized outcome adjudication committee consisting of a study neurologist,  
157 neurosurgeon, trauma surgeon and radiologist. The adjudicators will be blinded to all ED baseline data.  
158 Secondary outcomes relate to the 'severity' of the intracranial bleeding: 1) neurosurgical intervention; 2)  
159 intensive care admission; 3) hospital length of stay; 4) in-hospital death as determined by medical record  
160 review.  
161

162 We found poor sensitivity (37%, 95% confidence interval: 21 to 56%) for patient-reported diagnosis of  
163 intracranial bleeding.<sup>27</sup> Furthermore, our experience of personal follow up in this population<sup>28</sup> is that it is  
164 frequently not feasible because of residence in nursing homes or baseline cognitive impairment.  
165 Therefore, the current study follow up is restricted to systematic medical record review with  
166 independent validation and enrollment is restricted to patients who reside within the hospital  
167 catchment area.  
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3 **171 Predictor variables**

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5 172 Demographic and predictor variables are collected in two ways: 1) the treating physician completes a  
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7 173 standardized data collection form at the time of initial patient assessment, and before the results of the  
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9 174 head CT are available (therefore blinded to outcome); 2) data is collected by trained on-site research  
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11 175 assistants using standardized medical record review protocols, following detailed data definitions and  
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13 176 instructions for systematic medical record review. We follow standardized validation procedures for all  
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15 177 medical record review data points: de-identified source documentation is uploaded for validation by the  
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17 178 coordinating centre. A query is sent to the site research assistant to resolve each discrepancy. The study  
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19 179 site investigator resolves discrepancies which persist after research assistant review. Table 1 details the  
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21 180 demographic and predictor variables collected.  
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23 181

**Table 1: Description of collected demographic and predictor variables**

|  | Data collected by treating physician at initial assessment | Data collected by medical record review | Comment on predictor choice for rule derivation       |
|--|--|---|---|
| <b>Predictor variables</b>   |  |   |   |
| Age  |  | x                                       | No association found* but will be included            |
| Sex  |  | x                                       | Trend towards association with male sex*              |
| Head injury (as reported by patient or carer)                                | x  |   | Plausible higher risk                                 |
| Loss of consciousness  | x  |   | Marker for head injury severity                       |
| New amnesia about events of fall   | x  |   | Marker for head injury severity                       |
| History of previous major bleed <sup>28</sup>                                |  | x                                       | Trend towards association* and biologically plausible |
| Cirrhosis  |  | x                                       | Biologically plausible                                |
| Previous diagnosis of ischemic stroke  |  | x                                       | Biologically plausible                                |
| Chronic renal impairment   | x  | x                                       | Association demonstrated*                             |
| Reduced Glasgow Coma Score from normal (as indicated by caregiver or family) | x  |   | Association demonstrated*                             |

|  |   |   |  |
|--|---|---|--|
| Bruise or laceration on the head (any size)        | x |   | Association demonstrated*  |
| New abnormality on neurological examination        | x |   | Association demonstrated *   |
| Haemoglobin  |   | x | Biologically plausible   |
| Platelet count                                     |   | x | Biologically plausible   |
| Anticoagulation medication                         | x | x | Commonly held dogma  |
| Antiplatelet medication                            | x | x | Commonly held dogma  |
| Clinical Frailty Score <sup>30</sup>               | x |   | Biologically plausible   |
| <b>Descriptive variables</b>                       |   |   |  |
| Living circumstances                               |   | x | No association found*  |
| Diabetes   |   | x | No association found*  |
| Hypertension                                       |   | x | No association found*  |
| Active cancer within past 2 years                  |   | x | No association found*  |
| Dementia   |   | x | No association found*  |
| History of frequent falls                          |   | x | Not previously assessed*   |
| Congestive heart failure                           |   | x | No association found*  |
| Mechanism of injury                                |   | x | No association found*  |
| Weight   |   | x | No association found*  |
| Glasgow coma score at time of physician assessment | x |   | Reduced Glasgow Coma Score from normal has a stronger association* |
| Vomiting (once / more than once)                   | x |   | No association found*  |
| Signs of basal skull fracture                      | x |   | Too rare to assess*  |
| Suspected open or depressed skull fracture         | x |   | Too rare to assess*  |
| Retrograde amnesia for >30 minutes                 | x |   | Not previously assessed*   |

|                                      |  |   |                          |
|--------------------------------------|--|---|--------------------------|
| Creatinine                           |  | x | No association found*    |
| International normalized ratio (INR) |  | x | Anticipated missing data |

\* According to the results of our prior study,<sup>28</sup> N=1753

We initially identified potential predictor variables by a systematic review of prior evidence. We then assessed the frequency among our population and the association between predictor and intracranial bleeding in a study of 1753 older ED patients who had fallen.<sup>28</sup> We selected 17 candidate predictor variables, which are considered to be biologically plausible and related to the outcome of intracranial bleeding, and are routinely collected in the ED: age; sex; head injury; loss of consciousness; amnesia; history of previous major bleed (International Society of Thrombosis and Haemostasis criteria<sup>29</sup>); cirrhosis; prior ischemic stroke; chronic renal impairment; GCS reduced from baseline; bruise or laceration on the head; abnormal neurological examination; haemoglobin, platelet count; anticoagulant therapy; antiplatelet therapy; and, Clinical Frailty Score.<sup>30</sup>

### **Analysis**

Variables with large amounts of missing data will be excluded from the models as they would be missing in clinical practice. Likewise, continuous variables whose distributions are too narrow will also be excluded. We will perform binary recursive partitioning using Classification and Regression Trees to develop a decision rule. A clinical decision rule for a life-threatening event like intracranial bleeding requires very high sensitivity. The model with a sensitivity of > 99% and the highest specificity will be selected. We will assess the derived decision rule by comparing the classification of each patient with his or her actual status for the primary outcomes. In addition, 1000 bootstrap iterations will be performed to assess the internal classification performance and overfitting of the selected decision rule.

We will also develop a predictive risk model using multivariable logistic regression. Continuous variables may be transformed and will be fit using restricted cubic splines to relax the linearity assumption. First, a full model with all variables will be fit. To further reduce the model, we will perform backward elimination without model re-fitting with  $p < 0.5$ , which has shown to have valid inference.<sup>31,32</sup> Clinically and biologically plausible interactions will be tested within the model. Internal validation to obtain unbiased and optimism corrected estimation of model performance will be done using 1000 bootstrap

211 samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed  
212 versus predicted probabilities.

213

### 214 **Sample size**

215 The current guidelines suggest that we would require at least 10 events per included variable.<sup>33,34</sup> We  
216 expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,<sup>20</sup> and we  
217 assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample  
218 size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).

219

### 220 **Sources of bias**

221 Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is  
222 collected before the primary outcome data is collected. However, it is possible that we do not identify  
223 every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of  
224 patients had a head CT during the index ED visit.<sup>28</sup> Although patients are advised to return if they  
225 develop neurological symptoms, it is possible that a patient may die of an intracranial bleed before  
226 being diagnosed. Furthermore, 42-day follow-up involves institutional electronic medical record review.  
227 If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial  
228 bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study  
229 enrollment to patients who reside within the hospital catchment area and most sites have access to  
230 records from regional neurosurgical centres. In our prior study where we performed in-person follow  
231 up, no patient was diagnosed with an intracranial bleed at another hospital.

232

### 233 **Study oversight**

234 The coordinating centre is McMaster University. Electronic data and de-identified source documents are  
235 uploaded to a Research Electronic Data Capture (REDCap) database<sup>35,36</sup> and stored on a secure server at  
236 McMaster University. The coordinating centre validates all data and supervises the adjudication  
237 committee activities. The study steering committee consists of the site investigators.

238

### 239 **Ethics and dissemination**

240 Research ethics approval has been obtained from each enrolling site local research ethics board. In our  
241 previous study on the same population,<sup>28</sup> we obtained patient consent. An interim analysis showed a  
242 number of patients were confused (144/890, 16%) or died before a researcher could ask for their



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3 243 consent (39/890, 4%). Family were often not available in the ED. In all, we were unable to obtain  
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5 244 consent from 204/890 (23%) patients. To address this problem, we obtained research ethics board  
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7 245 approval to include patients who were unable to give informed consent. It is essential we include  
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9 246 patients who cannot consent since they are often the most frail patients who are challenging to evaluate  
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11 247 in the ED and frequently excluded from studies. Excluding these patients could limit the generalizability  
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13 248 of our clinical decision rule. The current study has research ethics approval at all sites to include patients  
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15 249 without obtaining informed consent.

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18 251 The study results will be submitted for publication in a peer reviewed journal and presented at national  
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20 252 and international emergency medicine meetings.

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3 254 **AUTHORS' CONTRIBUTIONS**

4 255 The study was conceived by KdW, MM, CK, SP and AW. The protocol was designed with input from  
5 256 all authors (KdW, MM, CK, SP, AW, NC, EM, ME, IS, DE, DB, RJ, JM, CV, SM, AP, YK, AS, SS and PE) has  
6 257 been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted  
7 258 by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee  
8 259 the analysis.  
9

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14 263  
15 264  
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## 281 REFERENCES

- 282
- 283 1. Van den Brand CL, Karger LB, Nijman ST, Hunink MG, Patka P, Jellema K. Traumatic brain injury
- 284 in the Netherlands, trends in emergency department visits, hospitalization and mortality
- 285 between 1998 and 2012. *Eur J Emerg Med.* 2017;06:06.
- 286 2. Haring RS, Narang K, Canner JK, et al. Traumatic brain injury in the elderly: morbidity and
- 287 mortality trends and risk factors. *J Surg Res.* 2015;195(1):1-9.
- 288 3. McIntyre A, Mehta S, Aubut J, Dijkers M, Teasell RW. Mortality among older adults after a
- 289 traumatic brain injury: A meta-analysis. *Brain Injury.* 2013;27(1):31-40.
- 290 4. Chan V, Colantonio A, Chen A, Zagorski B, Parsons D, Vander Laan R. A population based
- 291 perspective of acquired brain injury in older adults: How do they happen? *Brain Injury.* 2012;26
- 292 (4-5):548-549.
- 293 5. Kerr ZY, Harmon KJ, Marshall SW, Proescholdbell SK, Waller AE. The epidemiology of traumatic
- 294 brain injuries treated in emergency departments in North Carolina, 2010-2011. *N C Med J.*
- 295 2014;75(1):8-14.
- 296 6. Albrecht JS, Hirshon JM, McCunn M, et al. Increased rates of mild traumatic brain injury among
- 297 older adults in US Emergency Departments, 2009-2010. *Journal of Head Trauma Rehabilitation.*
- 298 2016;31(5):E1-E7.
- 299 7. Fu WW, Fu TS, Jing R, McFaul SR, Cusimano MD. Predictors of falls and mortality among elderly
- 300 adults with traumatic brain injury: A nationwide, population-based study. *PLoS ONE.* 2017;12 (4)
- 301 (no pagination)(e0175868).
- 302 8. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe.
- 303 *Acta Neurochirurgica.* 2015;157(10):1683-1696.
- 304 9. Hastings DL, Brieding M, Lee R. Falls and traumatic brain injuries in older adults: A worsening
- 305 trend. *Journal of the American Geriatrics Society.* 2017;65:S8.
- 306 10. Sung KC, Liang FW, Cheng TJ, Lu TH, Kawachi I. Trends in Unintentional Fall-Related Traumatic
- 307 Brain Injury Death Rates in Older Adults in the United States, 1980-2010: A Joinpoint Analysis. *J*
- 308 *Neurotrauma.* 2015;32(14):1078-1082.
- 309 11. Fletcher AE, Khalid S, Mallonee S. The epidemiology of severe traumatic brain injury among
- 310 persons 65 years of age and older in Oklahoma, 1992-2003. *Brain Injury.* 2007;21(7):691-699.
- 311 12. Chisholm KM, Harruff RC. Elderly deaths due to ground-level falls. *The American journal of*
- 312 *forensic medicine and pathology.* 2010;31(4):350-354.

- 1  
2  
3 313 13. Brazinova A, Mauritz W, Majdan M, Rehorcikova V, Leitgeb J. Fatal traumatic brain injury in  
4 314 older adults in Austria 1980-2012: an analysis of 33 years. *Age Ageing*. 2015;44(3):502-506.  
5 315 14. Shankar KN, Liu SW, Ganz DA. Trends and Characteristics of Emergency Department Visits for  
6 316 Fall-Related Injuries in Older Adults, 2003–2010. *Western Journal of Emergency Medicine*.  
7 317 2017;18(5):785-793.  
8 318 15. Hartholt KA, Van Lieshout EM, Polinder S, Panneman MJ, Van der Cammen TJ, Patka P. Rapid  
9 319 increase in hospitalizations resulting from fall-related traumatic head injury in older adults in  
10 320 The Netherlands 1986-2008. *J Neurotrauma*. 2011;28(5):739-744.  
11 321 16. Korhonen N, Niemi S, Parkkari J, Sievanen H, Kannus P. Incidence of fall-related traumatic brain  
12 322 injuries among older Finnish adults between 1970 and 2011. *Jama*. 2013;309(18):1891-1892.  
13 323 17. Verma SK, Willetts JL, Corns HL, Marucci-Wellman HR, Lombardi DA, Courtney TK. Falls and fall-  
14 324 related injuries among community-dwelling adults in the United States. *PLoS ONE*. 2016;11 (3)  
15 325 (no pagination)(e0150939).  
16 326 18. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor  
17 327 head injury. *The Lancet*. 2001;357(9266):1391-1396.  
18 328 19. de Wit K, Merali Z, Kagoma YK, Mercier É. Incidence of intracranial bleeding in seniors  
19 329 presenting to the emergency department after a fall: A systematic review. *Injury*.  
20 330 2020;51(2):157-163.  
21 331 20. Kelen G, Peterson S, Pronovost P. In the Name of Patient Safety, Lets Burden the Emergency  
22 332 Department More. *Annals of Emergency Medicine*.67(6):737-740.  
23 333 21. Émond M, Grenier D, Morin J, et al. Emergency Department Stay Associated Delirium in Older  
24 334 Patients. *Canadian Geriatrics Journal*. 2017;20(1):10-14.  
25 335 22. Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-spine rule for radiography in alert and  
26 336 stable trauma patients. *Jama*. 2001;286(15):1841-1848.  
27 337 23. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without  
28 338 diagnostic imaging: management of patients with suspected pulmonary embolism presenting to  
29 339 the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med*.  
30 340 2001;135(2):98-107.  
31 341 24. Thiruganasambandamoorthy V, Stiell IG, Sivilotti MLA, et al. Risk stratification of adult  
32 342 emergency department syncope patients to predict short-term serious outcomes after discharge  
33 343 (RiSEDS) study. *BMC Emergency Medicine*. 2014;14:8-8.

- 1  
2  
3 344 25. Stiehl IG, Wells GA. Methodologic standards for the development of clinical decision rules in  
4 345 emergency medicine. *Annals of Emergency Medicine*. 1999;33(4):437-447.  
5  
6 346 26. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable  
7 347 prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Annals*  
8 348 *of Internal Medicine* 2015;162(1):55-63.  
9  
10 349 27. Selvanayagam N, Soomro A, Varner C, McLeod S, Clayton N, de Wit K. LO59: Reliability of patient  
11 350 reported exposure and outcome data in a prospective cohort study of older adults presenting to  
12 351 the emergency department. *CJEM*. 2020;22(S1):S29-S29.  
13  
14 352 28. de Wit K, Parpia S, Varner C, et al. Clinical Predictors of Intracranial Bleeding in Older Adults  
15 353 Who Have Fallen: A Cohort Study. *Journal of the American Geriatrics Society*. 2020;68(5):970-  
16 354 976.  
17  
18 355 29. Schulman S, Kearon C, the SOCOAOTS, Standardization Committee Of The International Society  
19 356 On T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic  
20 357 medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis*.  
21 358 2005;3(4):692-694.  
22  
23 359 30. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly  
24 360 people. *Canadian Medical Association Journal*. 2005;173(5):489-495.  
25  
26 361 31. Lawless JF, Singhal K. Efficient Screening of Nonnormal Regression Models. *Biometrics*.  
27 362 1978;34(2):318-327.  
28  
29 363 32. Harrell F. *Regression Modeling Strategies With Applications to Linear Models, Logistic*  
30 364 *Regression, and Survival Analysis*. Springer New York; 2001.  
31  
32 365 33. Mallett S, Royston P, Dutton S, Waters R, Altman DG. Reporting methods in studies developing  
33 366 prognostic models in cancer: a review. *BMC Medicine*. 2010;8:20.  
34  
35 367 34. Pavlou M, Ambler G, Seaman SR, et al. How to develop a more accurate risk prediction model  
36 368 when there are few events. *BMJ (Clinical research ed)*. 2015;351:h3868.  
37  
38 369 35. PA Harris, R Taylor, R Thielke, J Payne, N Gonzalez, JG. Conde, Research electronic data capture  
39 370 (REDCap). A metadata-driven methodology and workflow process for providing translational  
40 371 research informatics support, *Journal of Biomedical Informatics*. 2009;42(2):377-81.  
41  
42 372 36. PA Harris, R Taylor, BL Minor, V Elliott, M Fernandez, L O'Neal, L McLeod, G Delacqua, F  
43 373 Delacqua, J Kirby, SN Duda, REDCap Consortium, The REDCap consortium: Building an  
44 374 international community of software partners, *Journal of Biomedical Informatics*. 2019,  
45 375 May [doi: 10.1016/j.jbi.2019.103208].  
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# BMJ Open

## Which older emergency patients are at risk of intracranial bleeding after a fall? A protocol to derive a clinical decision rule for the emergency department.

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## **Which older emergency patients are at risk of intracranial bleeding after a fall?**

### **A protocol to derive a clinical decision rule for the emergency department.**

Kerstin de Wit<sup>a,b</sup>, Mathew Mercuri<sup>a,c</sup>, Natasha Clayton<sup>a,d</sup>, Andrew Worster<sup>a,b</sup>, Éric Mercier<sup>e,f</sup>, Marcel Émond<sup>e,f</sup>, Catherine Varner<sup>g,h</sup>, Shelley McLeod<sup>g,h</sup>, Debra Eagles<sup>ij</sup>, Ian Stiell<sup>i</sup>, David Barbic<sup>k,l</sup>, Judy Morris<sup>m</sup>, Rebecca Jeanmonod<sup>n</sup>, Yoan Kagoma<sup>o</sup>, Ashkan Shoamanesh<sup>a</sup>, Paul Engels<sup>p</sup>, Sunjay Sharma<sup>q</sup>, Clive Kearon<sup>a</sup>, Alexandra Papaioannou<sup>a,b</sup>, Sameer Parpia<sup>b,r</sup>, for the Network of Canadian Emergency Researchers.

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3 34 **ABSTRACT**

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5 35 **Introduction**

6 36 Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide.  
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8 37 Older adults frequently present to the emergency department after falling. It can be challenging for  
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10 38 clinicians to determine who requires brain imaging to rule out traumatic intracranial bleeding, and often  
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12 39 head injury decision rules do not apply to older adults who fall. The goal of our study is to derive a  
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14 40 clinical decision rule which will identify older adults who present to the emergency department after a  
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16 41 fall who do not have clinically important intracranial bleeding.  
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19 43 **Methods and analysis**

20 44 This is a prospective cohort study enrolling patients aged 65 years or older, who present to the  
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22 45 emergency department of 11 hospitals in Canada and the United States within 48 hours of having a fall.  
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24 46 Patients are included if they fall on level ground, off a chair, toilet seat or out of bed. The primary  
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26 47 outcome is the diagnosis of clinically relevant intracranial bleeding within 42 days of the index  
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28 48 emergency department visit. An independent adjudication committee will determine the primary  
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30 50 treating physician completes a study data form at the time of initial assessment, prior to brain imaging.  
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32 51 Data extraction is supplemented by an independent, structured electronic medical record review. We  
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34 52 will perform binary recursive partitioning using Classification and Regression Trees to derive a clinical  
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36 53 decision rule.  
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39 55 **Ethics and dissemination**

40 56 The study was initially approved by Hamilton Integrated Research Ethics Committee and subsequently  
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42 57 approved by the research ethics boards governing all participating sites. We will disseminate our results  
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44 58 by journal publication, presentation at international meetings and social media.  
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47 60 **Registration details** ClinicalTrials.gov NCT03745755  
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3 64 **ARTICLE SUMMARY**  
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5 65 **Strengths and limitations of this study**  
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- 7 66 • This cohort study aims to derive a clinical decision rule which identifies older adults at risk of  
8 67 intracranial bleeding after a fall.  
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10 68 • This is a large study enrolling patients from 11 hospitals in two countries.  
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12 69 • Potential predictor variables are recorded by emergency physicians prior to CT scanning.  
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14 70 • The primary outcome, clinically important intracranial bleeding, is determined by an  
15 71 independent adjudication committee.  
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17 72 • The main limitation is that not all patients will have head CT imaging at their initial emergency  
18 73 department visit.  
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## 77 INTRODUCTION

78 In contrast to the younger population, the incidence of traumatic intracranial bleeding in older adults is  
79 rising<sup>1</sup> and has a worse prognosis.<sup>2,3</sup> Older adults are at higher risk of traumatic intracranial bleeding  
80 because there can be loss of the elastic integrity of the cerebral bridging veins and brain atrophy,  
81 allowing rapid movements of the brain within the cerebral spinal fluid with trauma. Older adults may be  
82 less able to withstand intracranial bleeding because of pre-existing comorbidity, frailty and  
83 polypharmacy.

84  
85 Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide,  
86 accounting for up to 80% of cases.<sup>4-8</sup> Fall-associated intracranial bleeding in older adults is increasing in  
87 incidence.<sup>9,10</sup> The mortality rate for fall-associated intracranial bleeding is 15%<sup>7,11</sup> (accounting for half of  
88 all fall-associated deaths<sup>12,13</sup>). Rather than seeing a decrease in these deaths, this mortality rate is  
89 rising.<sup>10</sup> Emergency departments (EDs) are managing an increasing number of older adults who have  
90 fallen<sup>14</sup> and ED visits for fall-related head injuries in older adults have increased year after year.<sup>9,13,15-17</sup>  
91 There is a paucity of evidence to guide neuroimaging for intracranial bleeding in older adults.

92  
93 The Canadian CT Head Rule can determine the need for head computed tomography (CT) in head-  
94 injured patients who experienced loss of consciousness, disorientation or amnesia after their injury.<sup>18</sup>  
95 However, older ED patients who present after a fall cannot always give a history of what happened, falls  
96 are frequently unwitnessed and many older adults who fall do not sustain a head injury. Ordering a head  
97 CT scan on every older adult who has fallen would be an inefficient and costly way to diagnose  
98 intracranial bleeding when only approximately 5% have intracranial bleeding.<sup>19</sup> Patients awaiting a CT  
99 scan will typically occupy an ED bed. CT overuse in this population not only causes prolonged ED visits,  
100 but it also contributes to ED overcrowding, which may result in worse outcomes for other patients.<sup>20</sup>  
101 Older adults are at greater risk of developing delirium the longer they stay in the ED.<sup>21</sup> There is a need  
102 for a simple bedside tool which can rapidly stratify the risk of intracranial bleeding in older ED patients  
103 who present after falling. Our aim is to derive a clinical decision rule which will identify older adults who  
104 present to the ED after a fall who do not have clinically important intracranial bleeding and therefore do  
105 not require a head CT.

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## 107 **METHODS AND ANALYSIS**

### 108 **Study design**

109 This is a prospective cohort study designed to develop a unique clinical decision rule for ED physicians  
110 evaluating older adults who have fallen. Clinical decision rules are a commonly applied method of  
111 standardized clinical diagnostic decision-making in the ED. The rules incorporate the standardized  
112 collection and interpretation of multiple predictor variables from the patient's history, physical  
113 examination and test results to optimize evidence-based clinical decision-making. For example, clinical  
114 decision rules are used to determine which patients should have cervical spine imaging in trauma,<sup>22</sup>  
115 thoracic imaging for pulmonary embolism<sup>23</sup> and admission after syncope.<sup>24</sup> Our study follows the  
116 methodological standards for clinical decision rules in emergency medicine<sup>25</sup> and the Transparent  
117 reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.<sup>26</sup>

### 119 **Patient and public involvement**

120 Prior to the protocol development, we conducted a qualitative study with older adults who were waiting  
121 in the ED for head CT after a fall. We found that diagnosing intracranial bleeding was important to the  
122 participants, that they valued testing tailored to their personal risk and shorter ED visits. This protocol  
123 was designed with feedback and input from our patient partners.

### 125 **Study population**

126 This study is conducted at 11 hospitals in Canada and the United States and enrolls patients aged 65  
127 years or older who present to the ED within 48 hours of having a fall. Patients are eligible if they fall on  
128 level ground (either inside or outside), off a chair, toilet seat or out of bed. Patients are included  
129 regardless of whether they hit their head. Patients are excluded if they fell down steps, fell from a  
130 height, were knocked down by a car/bike/pedestrian or other mechanism of injury. Patients who live  
131 outside of the hospital catchment area, who have previously been enrolled in this study, who are  
132 transferred from another hospital and who leave the ED prior to completion of their medical assessment  
133 are also excluded. Recruitment commenced on January 30, 2019. Patients are recruited 24 hours a day,  
134 seven days a week.

### 136 **Patient assessment**

137 Each patient is assessed at their index ED visit by an emergency physician who decides on the need for  
138 head CT based on clinical history and examination. It would be impractical to perform a head CT on all

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3 139 older adults who have fallen, for example, after a simple trip, because there is not always an indication  
4 140 for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if  
5 141 participants return to the ED within 42 days of enrolment with new confusion, headache, loss of  
6 142 balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological  
7 143 symptoms, they will undergo head CT.  
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### 145 **Outcome definition and measurement**

146 The primary outcome is '***clinically important intracranial bleeding***' diagnosed within 42 days of the  
147 index ED presentation. Our definition was derived after surveying specialists (including neurosurgeons,  
148 neurologists, trauma physicians, geriatricians, thrombosis and emergency physicians) who determined  
149 that symptoms from intracranial bleeding might develop as late as six weeks after a fall. 'Clinically  
150 important intracranial bleeding' is defined as bleeding within the cranial vault (including subdural,  
151 intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires  
152 medical or surgical treatment. Medical treatment is defined as any of the following: temporary or  
153 permanent discontinuation of anticoagulant or antiplatelet medication; administration of an  
154 antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation.  
155 Clinically important intracranial bleeding will be determined by independent adjudication of head CT  
156 scans by the centralized outcome adjudication committee consisting of a study neurologist,  
157 neurosurgeon, trauma surgeon and radiologist. The adjudicators will be blinded to all ED baseline data.  
158 Secondary outcomes relate to the 'severity' of the intracranial bleeding: 1) neurosurgical intervention; 2)  
159 intensive care admission; 3) hospital length of stay; 4) in-hospital death as determined by medical record  
160 review.  
161

162 We found poor sensitivity (37%, 95% confidence interval: 21 to 56%) for patient-reported diagnosis of  
163 intracranial bleeding.<sup>27</sup> Furthermore, our experience of personal follow up in this population<sup>28</sup> is that it is  
164 frequently not feasible because of residence in nursing homes or baseline cognitive impairment.  
165 Therefore, the current study follow up is restricted to systematic medical record review with  
166 independent validation and enrollment is restricted to patients who reside within the hospital  
167 catchment area.  
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3 **171 Predictor variables**

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5 172 Demographic and predictor variables are collected in two ways: 1) the treating physician completes a  
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7 173 standardized data collection form at the time of initial patient assessment, and before the results of the  
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9 174 head CT are available (therefore blinded to outcome); 2) data is collected by trained on-site research  
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11 175 assistants using standardized medical record review protocols, following detailed data definitions and  
12  
13 176 instructions for systematic medical record review. We follow standardized validation procedures for all  
14  
15 177 medical record review data points: de-identified source documentation is uploaded for validation by the  
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17 178 coordinating centre. A query is sent to the site research assistant to resolve each discrepancy. The study  
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19 179 site investigator resolves discrepancies which persist after research assistant review. Table 1 details the  
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21 180 demographic and predictor variables collected.  
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23 181

**Table 1: Description of collected demographic and predictor variables**

|  | Data collected by treating physician at initial assessment | Data collected by medical record review | Comment on predictor choice for rule derivation       |
|--|--|---|---|
| <b>Predictor variables</b>   |  |   |   |
| Age  |  | x                                       | No association found* but will be included            |
| Sex  |  | x                                       | Trend towards association with male sex*              |
| Head injury (as reported by patient or carer)                                | x  |   | Plausible higher risk                                 |
| Loss of consciousness  | x  |   | Marker for head injury severity                       |
| New amnesia about events of fall   | x  |   | Marker for head injury severity                       |
| History of previous major bleed <sup>28</sup>                                |  | x                                       | Trend towards association* and biologically plausible |
| Cirrhosis  |  | x                                       | Biologically plausible                                |
| Previous diagnosis of ischemic stroke  |  | x                                       | Biologically plausible                                |
| Chronic renal impairment   | x  | x                                       | Association demonstrated*                             |
| Reduced Glasgow Coma Score from normal (as indicated by caregiver or family) | x  |   | Association demonstrated*                             |



|  |   |   |  |
|--|---|---|--|
| Bruise or laceration on the head (any size)        | x |   | Association demonstrated*  |
| New abnormality on neurological examination        | x |   | Association demonstrated *   |
| Haemoglobin  |   | x | Biologically plausible   |
| Platelet count                                     |   | x | Biologically plausible   |
| Anticoagulation medication                         | x | x | Commonly held dogma  |
| Antiplatelet medication                            | x | x | Commonly held dogma  |
| Clinical Frailty Score <sup>30</sup>               | x |   | Biologically plausible   |
| <b>Descriptive variables</b>                       |   |   |  |
| Living circumstances                               |   | x | No association found*  |
| Diabetes   |   | x | No association found*  |
| Hypertension                                       |   | x | No association found*  |
| Active cancer within past 2 years                  |   | x | No association found*  |
| Dementia   |   | x | No association found*  |
| History of frequent falls                          |   | x | Not previously assessed*   |
| Congestive heart failure                           |   | x | No association found*  |
| Mechanism of injury                                |   | x | No association found*  |
| Weight   |   | x | No association found*  |
| Glasgow coma score at time of physician assessment | x |   | Reduced Glasgow Coma Score from normal has a stronger association* |
| Vomiting (once / more than once)                   | x |   | No association found*  |
| Signs of basal skull fracture                      | x |   | Too rare to assess*  |
| Suspected open or depressed skull fracture         | x |   | Too rare to assess*  |
| Retrograde amnesia for >30 minutes                 | x |   | Not previously assessed*   |

|                                      |  |   |                          |
|--------------------------------------|--|---|--------------------------|
| Creatinine                           |  | x | No association found*    |
| International normalized ratio (INR) |  | x | Anticipated missing data |

\* According to the results of our prior study,<sup>28</sup> N=1753

We initially identified potential predictor variables by a systematic review of prior evidence. We then assessed the frequency among our population and the association between predictor and intracranial bleeding in a study of 1753 older ED patients who had fallen.<sup>28</sup> We selected 17 candidate predictor variables, which are considered to be biologically plausible and related to the outcome of intracranial bleeding, and are routinely collected in the ED: age; sex; head injury; loss of consciousness; amnesia; history of previous major bleed (International Society of Thrombosis and Haemostasis criteria<sup>29</sup>); cirrhosis; prior ischemic stroke; chronic renal impairment; GCS reduced from baseline; bruise or laceration on the head; abnormal neurological examination; haemoglobin, platelet count; anticoagulant therapy; antiplatelet therapy; and, Clinical Frailty Score.<sup>30</sup>

### **Analysis**

Variables with large amounts of missing data will be excluded from the models as they would be missing in clinical practice. Likewise, continuous variables whose distributions are too narrow will also be excluded. We will perform binary recursive partitioning using Classification and Regression Trees to develop a decision rule. A clinical decision rule for a life-threatening event like intracranial bleeding requires very high sensitivity. The model with a sensitivity of > 99% and the highest specificity will be selected. We will assess the derived decision rule by comparing the classification of each patient with his or her actual status for the primary outcomes. In addition, 1000 bootstrap iterations will be performed to assess the internal classification performance and overfitting of the selected decision rule.

We will also develop a predictive risk model using multivariable logistic regression. Continuous variables may be transformed and will be fit using restricted cubic splines to relax the linearity assumption. First, a full model with all variables will be fit. To further reduce the model, we will perform backward elimination without model re-fitting with  $p < 0.5$ , which has shown to have valid inference.<sup>31,32</sup> Clinically and biologically plausible interactions will be tested within the model. Internal validation to obtain unbiased and optimism corrected estimation of model performance will be done using 1000 bootstrap

211 samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed  
212 versus predicted probabilities.

213

### 214 **Sample size**

215 The current guidelines suggest that we would require at least 10 events per included variable.<sup>33,34</sup> We  
216 expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,<sup>20</sup> and we  
217 assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample  
218 size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).

219

### 220 **Sources of bias**

221 Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is  
222 collected before the primary outcome data is collected. However, it is possible that we do not identify  
223 every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of  
224 patients had a head CT during the index ED visit.<sup>28</sup> Although patients are advised to return if they  
225 develop neurological symptoms, it is possible that a patient may die of an intracranial bleed before  
226 being diagnosed. Furthermore, 42-day follow-up involves institutional electronic medical record review.  
227 If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial  
228 bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study  
229 enrollment to patients who reside within the hospital catchment area and most sites have access to  
230 records from regional neurosurgical centres. In our prior study where we performed in-person follow  
231 up, no patient was diagnosed with an intracranial bleed at another hospital.

232

### 233 **Study oversight**

234 The coordinating centre is McMaster University. Electronic data and de-identified source documents are  
235 uploaded to a Research Electronic Data Capture (REDCap) database<sup>35,36</sup> and stored on a secure server at  
236 McMaster University. The coordinating centre validates all data and supervises the adjudication  
237 committee activities. The study steering committee consists of the site investigators.

238

### 239 **Ethics and dissemination**

240 Research ethics approval has been obtained from each enrolling site local research ethics board. In our  
241 previous study on the same population,<sup>28</sup> we obtained patient consent. An interim analysis showed a  
242 number of patients were confused (144/890, 16%) or died before a researcher could ask for their

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3 243 consent (39/890, 4%). Family were often not available in the ED. In all, we were unable to obtain  
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5 244 consent from 204/890 (23%) patients. To address this problem, we obtained research ethics board  
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7 245 approval to include patients who were unable to give informed consent. It is essential we include  
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9 246 patients who cannot consent since they are often the most frail patients who are challenging to evaluate  
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11 247 in the ED and frequently excluded from studies. Excluding these patients could limit the generalizability  
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13 248 of our clinical decision rule. The current study has research ethics approval at all sites to include patients  
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15 249 without obtaining informed consent.

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18 251 The study results will be submitted for publication in a peer reviewed journal and presented at national  
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20 252 and international emergency medicine meetings.

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3 254 **AUTHORS' CONTRIBUTIONS**

4 255 The study was conceived by KdW, MM, CK, SP and AW. The protocol was designed with input from  
5 256 all authors (KdW, MM, CK, SP, AW, NC, EM, ME, IS, DE, DB, RJ, JM, CV, SM, AP, YK, AS, SS and PE) has  
6 257 been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted  
7 258 by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee  
8 259 the analysis.  
9

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14 263  
15 264  
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## 281 REFERENCES

- 282
- 283 1. Van den Brand CL, Karger LB, Nijman ST, Hunink MG, Patka P, Jellema K. Traumatic brain injury
- 284 in the Netherlands, trends in emergency department visits, hospitalization and mortality
- 285 between 1998 and 2012. *Eur J Emerg Med.* 2017;06:06.
- 286 2. Haring RS, Narang K, Canner JK, et al. Traumatic brain injury in the elderly: morbidity and
- 287 mortality trends and risk factors. *J Surg Res.* 2015;195(1):1-9.
- 288 3. McIntyre A, Mehta S, Aubut J, Dijkers M, Teasell RW. Mortality among older adults after a
- 289 traumatic brain injury: A meta-analysis. *Brain Injury.* 2013;27(1):31-40.
- 290 4. Chan V, Colantonio A, Chen A, Zagorski B, Parsons D, Vander Laan R. A population based
- 291 perspective of acquired brain injury in older adults: How do they happen? *Brain Injury.* 2012;26
- 292 (4-5):548-549.
- 293 5. Kerr ZY, Harmon KJ, Marshall SW, Proescholdbell SK, Waller AE. The epidemiology of traumatic
- 294 brain injuries treated in emergency departments in North Carolina, 2010-2011. *N C Med J.*
- 295 2014;75(1):8-14.
- 296 6. Albrecht JS, Hirshon JM, McCunn M, et al. Increased rates of mild traumatic brain injury among
- 297 older adults in US Emergency Departments, 2009-2010. *Journal of Head Trauma Rehabilitation.*
- 298 2016;31(5):E1-E7.
- 299 7. Fu WW, Fu TS, Jing R, McFaul SR, Cusimano MD. Predictors of falls and mortality among elderly
- 300 adults with traumatic brain injury: A nationwide, population-based study. *PLoS ONE.* 2017;12 (4)
- 301 (no pagination)(e0175868).
- 302 8. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe.
- 303 *Acta Neurochirurgica.* 2015;157(10):1683-1696.
- 304 9. Hastings DL, Brieding M, Lee R. Falls and traumatic brain injuries in older adults: A worsening
- 305 trend. *Journal of the American Geriatrics Society.* 2017;65:S8.
- 306 10. Sung KC, Liang FW, Cheng TJ, Lu TH, Kawachi I. Trends in Unintentional Fall-Related Traumatic
- 307 Brain Injury Death Rates in Older Adults in the United States, 1980-2010: A Joinpoint Analysis. *J*
- 308 *Neurotrauma.* 2015;32(14):1078-1082.
- 309 11. Fletcher AE, Khalid S, Mallonee S. The epidemiology of severe traumatic brain injury among
- 310 persons 65 years of age and older in Oklahoma, 1992-2003. *Brain Injury.* 2007;21(7):691-699.
- 311 12. Chisholm KM, Harruff RC. Elderly deaths due to ground-level falls. *The American journal of*
- 312 *forensic medicine and pathology.* 2010;31(4):350-354.

- 1  
2  
3 313 13. Brazinova A, Mauritz W, Majdan M, Rehorcikova V, Leitgeb J. Fatal traumatic brain injury in  
4 314 older adults in Austria 1980-2012: an analysis of 33 years. *Age Ageing*. 2015;44(3):502-506.  
5 315 14. Shankar KN, Liu SW, Ganz DA. Trends and Characteristics of Emergency Department Visits for  
6 316 Fall-Related Injuries in Older Adults, 2003–2010. *Western Journal of Emergency Medicine*.  
7 317 2017;18(5):785-793.  
8 318 15. Hartholt KA, Van Lieshout EM, Polinder S, Panneman MJ, Van der Cammen TJ, Patka P. Rapid  
9 319 increase in hospitalizations resulting from fall-related traumatic head injury in older adults in  
10 320 The Netherlands 1986-2008. *J Neurotrauma*. 2011;28(5):739-744.  
11 321 16. Korhonen N, Niemi S, Parkkari J, Sievanen H, Kannus P. Incidence of fall-related traumatic brain  
12 322 injuries among older Finnish adults between 1970 and 2011. *Jama*. 2013;309(18):1891-1892.  
13 323 17. Verma SK, Willetts JL, Corns HL, Marucci-Wellman HR, Lombardi DA, Courtney TK. Falls and fall-  
14 324 related injuries among community-dwelling adults in the United States. *PLoS ONE*. 2016;11 (3)  
15 325 (no pagination)(e0150939).  
16 326 18. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor  
17 327 head injury. *The Lancet*. 2001;357(9266):1391-1396.  
18 328 19. de Wit K, Merali Z, Kagoma YK, Mercier É. Incidence of intracranial bleeding in seniors  
19 329 presenting to the emergency department after a fall: A systematic review. *Injury*.  
20 330 2020;51(2):157-163.  
21 331 20. Kelen G, Peterson S, Pronovost P. In the Name of Patient Safety, Lets Burden the Emergency  
22 332 Department More. *Annals of Emergency Medicine*. 67(6):737-740.  
23 333 21. Émond M, Grenier D, Morin J, et al. Emergency Department Stay Associated Delirium in Older  
24 334 Patients. *Canadian Geriatrics Journal*. 2017;20(1):10-14.  
25 335 22. Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-spine rule for radiography in alert and  
26 336 stable trauma patients. *Jama*. 2001;286(15):1841-1848.  
27 337 23. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without  
28 338 diagnostic imaging: management of patients with suspected pulmonary embolism presenting to  
29 339 the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med*.  
30 340 2001;135(2):98-107.  
31 341 24. Thiruganasambandamoorthy V, Stiell IG, Sivilotti MLA, et al. Risk stratification of adult  
32 342 emergency department syncope patients to predict short-term serious outcomes after discharge  
33 343 (RiSEDS) study. *BMC Emergency Medicine*. 2014;14:8-8.

- 1  
2  
3 344 25. Stiehl IG, Wells GA. Methodologic standards for the development of clinical decision rules in  
4 345 emergency medicine. *Annals of Emergency Medicine*. 1999;33(4):437-447.  
5  
6 346 26. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable  
7 347 prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Annals*  
8 348 of Internal Medicine 2015;162(1):55-63.  
9  
10 349 27. Selvanayagam N, Soomro A, Varner C, McLeod S, Clayton N, de Wit K. LO59: Reliability of patient  
11 350 reported exposure and outcome data in a prospective cohort study of older adults presenting to  
12 351 the emergency department. *CJEM*. 2020;22(S1):S29-S29.  
13  
14 352 28. de Wit K, Parpia S, Varner C, et al. Clinical Predictors of Intracranial Bleeding in Older Adults  
15 353 Who Have Fallen: A Cohort Study. *Journal of the American Geriatrics Society*. 2020;68(5):970-  
16 354 976.  
17  
18 355 29. Schulman S, Kearon C, the SOCOAOTS, Standardization Committee Of The International Society  
19 356 On T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic  
20 357 medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis*.  
21 358 2005;3(4):692-694.  
22  
23 359 30. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly  
24 360 people. *Canadian Medical Association Journal*. 2005;173(5):489-495.  
25  
26 361 31. Lawless JF, Singhal K. Efficient Screening of Nonnormal Regression Models. *Biometrics*.  
27 362 1978;34(2):318-327.  
28  
29 363 32. Harrell F. *Regression Modeling Strategies With Applications to Linear Models, Logistic*  
30 364 *Regression, and Survival Analysis*. Springer New York; 2001.  
31  
32 365 33. Mallett S, Royston P, Dutton S, Waters R, Altman DG. Reporting methods in studies developing  
33 366 prognostic models in cancer: a review. *BMC Medicine*. 2010;8:20.  
34  
35 367 34. Pavlou M, Ambler G, Seaman SR, et al. How to develop a more accurate risk prediction model  
36 368 when there are few events. *BMJ (Clinical research ed)*. 2015;351:h3868.  
37  
38 369 35. PA Harris, R Taylor, R Thielke, J Payne, N Gonzalez, JG. Conde, Research electronic data capture  
39 370 (REDCap). A metadata-driven methodology and workflow process for providing translational  
40 371 research informatics support, *Journal of Biomedical Informatics*. 2009;42(2):377-81.  
41  
42 372 36. PA Harris, R Taylor, BL Minor, V Elliott, M Fernandez, L O'Neal, L McLeod, G Delacqua, F  
43 373 Delacqua, J Kirby, SN Duda, REDCap Consortium, The REDCap consortium: Building an  
44 374 international community of software partners, *Journal of Biomedical Informatics*. 2019,  
45 375 May [doi: 10.1016/j.jbi.2019.103208].  
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# BMJ Open

## Which older emergency patients are at risk of intracranial bleeding after a fall? A protocol to derive a clinical decision rule for the emergency department.

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## **Which older emergency patients are at risk of intracranial bleeding after a fall?**

### **A protocol to derive a clinical decision rule for the emergency department.**

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For peer review only

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3 34 **ABSTRACT**

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5 35 **Introduction**

6 36 Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide.  
7  
8 37 Older adults frequently present to the emergency department after falling. It can be challenging for  
9  
10 38 clinicians to determine who requires brain imaging to rule out traumatic intracranial bleeding, and often  
11  
12 39 head injury decision rules do not apply to older adults who fall. The goal of our study is to derive a  
13  
14 40 clinical decision rule which will identify older adults who present to the emergency department after a  
15  
16 41 fall who do not have clinically important intracranial bleeding.  
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18 42  
19 43 **Methods and analysis**

20 44 This is a prospective cohort study enrolling patients aged 65 years or older, who present to the  
21  
22 45 emergency department of 11 hospitals in Canada and the United States within 48 hours of having a fall.  
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24 46 Patients are included if they fall on level ground, off a chair, toilet seat or out of bed. The primary  
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26 47 outcome is the diagnosis of clinically relevant intracranial bleeding within 42 days of the index  
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28 48 emergency department visit. An independent adjudication committee will determine the primary  
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30 49 outcome, blinded to all other data. We are collecting data on 17 potential predictor variables. The  
31  
32 50 treating physician completes a study data form at the time of initial assessment, prior to brain imaging.  
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34 51 Data extraction is supplemented by an independent, structured electronic medical record review. We  
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36 52 will perform binary recursive partitioning using Classification and Regression Trees to derive a clinical  
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38 53 decision rule.  
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40 54  
41 55 **Ethics and dissemination**

42 56 The study was initially approved by Hamilton Integrated Research Ethics Committee and subsequently  
43  
44 57 approved by the research ethics boards governing all participating sites. We will disseminate our results  
45  
46 58 by journal publication, presentation at international meetings and social media.  
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49 60 **Registration details** ClinicalTrials.gov NCT03745755  
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3 64 **ARTICLE SUMMARY**  
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5 65 **Strengths and limitations of this study**  
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- 7 66 • This cohort study aims to derive a clinical decision rule which identifies older adults at risk of  
8 67 intracranial bleeding after a fall.  
9  
10 68 • This is a large study enrolling patients from 11 hospitals in two countries.  
11  
12 69 • Potential predictor variables are recorded by emergency physicians prior to CT scanning.  
13  
14 70 • The primary outcome, clinically important intracranial bleeding, is determined by an  
15 71 independent adjudication committee.  
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17 72 • The main limitation is that not all patients will have head CT imaging at their initial emergency  
18 73 department visit.  
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## 77 INTRODUCTION

78 In contrast to the younger population, the incidence of traumatic intracranial bleeding in older adults is  
79 rising<sup>1</sup> and has a worse prognosis.<sup>2,3</sup> Older adults are at higher risk of traumatic intracranial bleeding  
80 because there can be loss of the elastic integrity of the cerebral bridging veins and brain atrophy,  
81 allowing rapid movements of the brain within the cerebral spinal fluid with trauma. Older adults may be  
82 less able to withstand intracranial bleeding because of pre-existing comorbidity, frailty and  
83 polypharmacy.

84  
85 Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide,  
86 accounting for up to 80% of cases.<sup>4-8</sup> Fall-associated intracranial bleeding in older adults is increasing in  
87 incidence.<sup>9,10</sup> The mortality rate for fall-associated intracranial bleeding is 15%<sup>7,11</sup> (accounting for half of  
88 all fall-associated deaths<sup>12,13</sup>). Rather than seeing a decrease in these deaths, this mortality rate is  
89 rising.<sup>10</sup> Emergency departments (EDs) are managing an increasing number of older adults who have  
90 fallen<sup>14</sup> and ED visits for fall-related head injuries in older adults have increased year after year.<sup>9,13,15-17</sup>  
91 There is a paucity of evidence to guide neuroimaging for intracranial bleeding in older adults.

92  
93 The Canadian CT Head Rule can determine the need for head computed tomography (CT) in head-  
94 injured patients who experienced loss of consciousness, disorientation or amnesia after their injury.<sup>18</sup>  
95 However, older ED patients who present after a fall cannot always give a history of what happened, falls  
96 are frequently unwitnessed and many older adults who fall do not sustain a head injury. Ordering a head  
97 CT scan on every older adult who has fallen would be an inefficient and costly way to diagnose  
98 intracranial bleeding when only approximately 5% have intracranial bleeding.<sup>19</sup> Patients awaiting a CT  
99 scan will typically occupy an ED bed. CT overuse in this population not only causes prolonged ED visits,  
100 but it also contributes to ED overcrowding, which may result in worse outcomes for other patients.<sup>20</sup>  
101 Older adults are at greater risk of developing delirium the longer they stay in the ED.<sup>21</sup> There is a need  
102 for a simple bedside tool which can rapidly stratify the risk of intracranial bleeding in older ED patients  
103 who present after falling. Our aim is to derive a clinical decision rule which will identify older adults who  
104 present to the ED after a fall who do not have clinically important intracranial bleeding and therefore do  
105 not require a head CT.

106



## 107 **METHODS AND ANALYSIS**

### 108 **Study design**

109 This is a prospective cohort study designed to develop a unique clinical decision rule for ED physicians  
110 evaluating older adults who have fallen. Clinical decision rules are a commonly applied method of  
111 standardized clinical diagnostic decision-making in the ED. The rules incorporate the standardized  
112 collection and interpretation of multiple predictor variables from the patient's history, physical  
113 examination and test results to optimize evidence-based clinical decision-making. For example, clinical  
114 decision rules are used to determine which patients should have cervical spine imaging in trauma,<sup>22</sup>  
115 thoracic imaging for pulmonary embolism<sup>23</sup> and admission after syncope.<sup>24</sup> Our study follows the  
116 methodological standards for clinical decision rules in emergency medicine<sup>25</sup> and the Transparent  
117 reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.<sup>26</sup>

118  
119 The study was approved by the Hamilton Integrated Research Ethics Board, Ottawa Health Science  
120 Network Research Ethics Board, Mount Sinai Hospital Research Ethics Board, Comité d'éthique du CHU  
121 de Québec-Université Laval, Providence Health Care Research Ethics Board and the Institutional Review  
122 Board of St. Luke's University Health Network.

### 124 **Patient and public involvement**

125 Prior to the protocol development, we conducted a qualitative study with older adults who were waiting  
126 in the ED for head CT after a fall. We found that diagnosing intracranial bleeding was important to the  
127 participants, that they valued testing tailored to their personal risk and shorter ED visits. This protocol  
128 was designed with feedback and input from our patient partners.

### 130 **Study population**

131 This study is conducted at 11 hospitals in Canada and the United States and enrolls patients aged 65  
132 years or older who present to the ED within 48 hours of having a fall. Patients are eligible if they fall on  
133 level ground (either inside or outside), off a chair, toilet seat or out of bed. Patients are included  
134 regardless of whether they hit their head. Patients are excluded if they fell down steps, fell from a  
135 height, were knocked down by a car/bike/pedestrian or other mechanism of injury. Patients who live  
136 outside of the hospital catchment area, who have previously been enrolled in this study, who are  
137 transferred from another hospital and who leave the ED prior to completion of their medical assessment

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2  
3 138 are also excluded. Recruitment commenced on January 30, 2019. Patients are recruited 24 hours a day,  
4  
5 139 seven days a week.

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### 8 141 **Patient assessment**

9  
10 142 Each patient is assessed at their index ED visit by an emergency physician who decides on the need for  
11  
12 143 head CT based on clinical history and examination. It would be impractical to perform a head CT on all  
13  
14 144 older adults who have fallen, for example, after a simple trip, because there is not always an indication  
15  
16 145 for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if  
17  
18 146 participants return to the ED within 42 days of enrolment with new confusion, headache, loss of  
19  
20 147 balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological  
21  
22 148 symptoms, they will undergo head CT.

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### 25 150 **Outcome definition and measurement**

26 151 The primary outcome is '***clinically important intracranial bleeding***' diagnosed within 42 days of the  
27  
28 152 index ED presentation. Our definition was derived after surveying specialists (including neurosurgeons,  
29  
30 153 neurologists, trauma physicians, geriatricians, thrombosis and emergency physicians) who determined  
31  
32 154 that symptoms from intracranial bleeding might develop as late as six weeks after a fall. 'Clinically  
33  
34 155 important intracranial bleeding' is defined as bleeding within the cranial vault (including subdural,  
35  
36 156 intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires  
37  
38 157 medical or surgical treatment. Medical treatment is defined as any of the following: temporary or  
39  
40 158 permanent discontinuation of anticoagulant or antiplatelet medication; administration of an  
41  
42 159 antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation.  
43  
44 160 Clinically important intracranial bleeding will be determined by independent adjudication of head CT  
45  
46 161 scans by the centralized outcome adjudication committee consisting of a study neurologist,  
47  
48 162 neurosurgeon, trauma surgeon and radiologist. The adjudicators will be blinded to all ED baseline data.  
49  
50 163 Each scan will be adjudicated independently by two reviewers. In the case of a disagreement, a third  
51  
52 164 adjudicator, blinded to the prior reviews, will determine the classification. Agreement between the  
53  
54 165 adjudicators will be reported. Secondary outcomes relate to the 'severity' of the intracranial bleeding: 1)  
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56 166 neurosurgical intervention; 2) intensive care admission; 3) hospital length of stay; 4) in-hospital death as  
57  
58 167 determined by medical record review.

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3 169 We found poor sensitivity (37%, 95% confidence interval: 21 to 56%) for patient-reported diagnosis of  
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5 170 intracranial bleeding.<sup>27</sup> Furthermore, our experience of personal follow up in this population<sup>28</sup> is that it is  
6  
7 171 frequently not feasible because of residence in nursing homes or baseline cognitive impairment.  
8  
9 172 Therefore, the current study follow up is restricted to systematic medical record review with  
10  
11 173 independent validation and enrollment is restricted to patients who reside within the hospital  
12  
13 174 catchment area.

13 175

### 15 176 **Predictor variables**

16  
17 177 Demographic and predictor variables are collected in two ways: 1) the treating physician completes a  
18  
19 178 standardized data collection form at the time of initial patient assessment, and before the results of the  
20  
21 179 head CT are available (therefore blinded to outcome); 2) data is collected by trained on-site research  
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23 180 assistants using standardized medical record review protocols, following detailed data definitions and  
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25 181 instructions for systematic medical record review. We follow standardized validation procedures for all  
26  
27 182 medical record review data points: de-identified source documentation is uploaded for validation by the  
28  
29 183 coordinating centre. A query is sent to the site research assistant to resolve each discrepancy. The study  
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31 184 site investigator resolves discrepancies which persist after research assistant review. Table 1 details the  
32  
33 185 demographic and predictor variables collected.

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33  
34 187 We initially identified potential predictor variables by a systematic review of prior evidence. We then  
35  
36 188 assessed the frequency among our population and the association between predictor and intracranial  
37  
38 189 bleeding in a study of 1753 older ED patients who had fallen.<sup>28</sup> We selected 17 candidate predictor  
39  
40 190 variables, which are considered to be biologically plausible and related to the outcome of intracranial  
41  
42 191 bleeding, and are routinely collected in the ED: age; sex; head injury; loss of consciousness; amnesia;  
43  
44 192 history of previous major bleed (International Society of Thrombosis and Haemostasis criteria<sup>29</sup>);  
45  
46 193 cirrhosis; prior ischemic stroke; chronic renal impairment; GCS reduced from baseline; bruise or  
47  
48 194 laceration on the head; abnormal neurological examination; haemoglobin, platelet count; anticoagulant  
49  
50 195 therapy; antiplatelet therapy; and, Clinical Frailty Score.<sup>30</sup>

49 196

### 50 197 **Analysis**

51  
52 198 Variables with large amounts of missing data will be excluded from the models as they would be missing  
53  
54 199 in clinical practice. Likewise, continuous variables whose distributions are too narrow will also be  
55  
56 200 excluded. We will perform binary recursive partitioning using Classification and Regression Trees to

201 develop a decision rule. A clinical decision rule for a life-threatening event like intracranial bleeding  
202 requires very high sensitivity. The model with a sensitivity of > 99% and the highest specificity will be  
203 selected. We will assess the derived decision rule by comparing the classification of each patient with his  
204 or her actual status for the primary outcomes. In addition, 1000 bootstrap iterations will be performed  
205 to assess the internal classification performance and overfitting of the selected decision rule.

206  
207 We will also develop a predictive risk model using multivariable logistic regression. Continuous variables  
208 may be transformed and will be fit using restricted cubic splines to relax the linearity assumption. First, a  
209 full model with all variables will be fit. To further reduce the model, we will perform backward  
210 elimination without model re-fitting with  $p < 0.5$ , which has shown to have valid inference.<sup>31,32</sup> Clinically  
211 and biologically plausible interactions will be tested within the model. Internal validation to obtain  
212 unbiased and optimism corrected estimation of model performance will be done using 1000 bootstrap  
213 samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed  
214 versus predicted probabilities.

#### 215 216 **Sample size**

217 The current guidelines suggest that we would require at least 10 events per included variable.<sup>33,34</sup> We  
218 expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,<sup>20</sup> and we  
219 assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample  
220 size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).

#### 221 222 **Sources of bias**

223 Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is  
224 collected before the primary outcome data is collected. However, it is possible that we do not identify  
225 every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of  
226 patients had a head CT during the index ED visit and 6/738 participants without a head CT (0.8%) were  
227 subsequently diagnosed with intracranial bleeding within 42 days.<sup>28</sup> In comparison, 6/939 (0.6%) with a  
228 negative head CT were diagnosed with intracranial bleeding within 42 days, suggesting emergency  
229 physicians may correctly identify lower risk patients who do not require a scan. However, this evidence  
230 is indirect and hypothesis generating only. Given that not all participants in this study will have a head  
231 CT scan at baseline, we may underdiagnose intracranial bleeding in this subpopulation which will  
232 comprise around 40% of the cohort. Although patients are advised to return if they develop

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3 233 neurological symptoms, it is possible that a patient may die of an intracranial bleed or else fully recover  
4 234 without testing for intracranial bleeding. Furthermore, 42-day follow-up involves institutional electronic  
5 235 medical record review. If a patient attended an unrelated hospital during follow up and was diagnosed  
6 236 with an intracranial bleed, we might miss this diagnosis. To reduce the chance of this happening, we are  
7 237 restricting study enrollment to patients who reside within the hospital catchment area and most sites  
8 238 have access to records from regional neurosurgical centres. In our prior study where we performed in-  
9 239 person follow up, no patient was diagnosed with an intracranial bleed at another hospital. The imperfect  
10 240 reference standard bias introduced with differential testing depending on the emergency physician CT  
11 241 request, might inflate the strength of association between predictor variables which are commonly  
12 242 utilized to determine the need for head CT in this population (such as a history of loss of consciousness  
13 243 and anticoagulation use).  
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### 23 245 **Study oversight**

24 246 The coordinating centre is McMaster University. Electronic data and de-identified source documents are  
25 247 uploaded to a Research Electronic Data Capture (REDCap) database<sup>35,36</sup> and stored on a secure server at  
26 248 McMaster University. The coordinating centre validates all data and supervises the adjudication  
27 249 committee activities. The study steering committee consists of the site investigators.  
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### 33 251 **Ethics and dissemination**

34 252 Research ethics approval has been obtained from each enrolling site local research ethics board. In our  
35 253 previous study on the same population,<sup>28</sup> we obtained patient consent. An interim analysis showed a  
36 254 number of patients were confused (144/890, 16%) or died before a researcher could ask for their  
37 255 consent (39/890, 4%). Family were often not available in the ED. In all, we were unable to obtain  
38 256 consent from 204/890 (23%) patients. To address this problem, we obtained research ethics board  
39 257 approval to include patients who were unable to give informed consent. It is essential we include  
40 258 patients who cannot consent since they are often the most frail patients who are challenging to evaluate  
41 259 in the ED and frequently excluded from studies. Excluding these patients could limit the generalizability  
42 260 of our clinical decision rule. The current study has research ethics approval at all sites to include patients  
43 261 without obtaining informed consent.  
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53 263 The study results will be submitted for publication in a peer reviewed journal and presented at national  
54 264 and international emergency medicine meetings.  
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3 265 **AUTHORS' CONTRIBUTIONS**

4 266 The study was conceived by KdW, MM, CK, SP and AW. The protocol was designed with input from  
5 267 all authors (KdW, MM, CK, SP, AW, NC, EM, ME, IS, DE, DB, RJ, JM, CV, SM, AP, YK, AS, SS and PE) has  
6 268 been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted  
7 269 by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee  
8 270 the analysis.  
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## 292 REFERENCES

- 293
- 294 1. Van den Brand CL, Karger LB, Nijman ST, Hunink MG, Patka P, Jellema K. Traumatic brain injury  
295 in the Netherlands, trends in emergency department visits, hospitalization and mortality  
296 between 1998 and 2012. *Eur J Emerg Med.* 2017;06:06.
- 297 2. Haring RS, Narang K, Canner JK, et al. Traumatic brain injury in the elderly: morbidity and  
298 mortality trends and risk factors. *J Surg Res.* 2015;195(1):1-9.
- 299 3. McIntyre A, Mehta S, Aubut J, Dijkers M, Teasell RW. Mortality among older adults after a  
300 traumatic brain injury: A meta-analysis. *Brain Injury.* 2013;27(1):31-40.
- 301 4. Chan V, Colantonio A, Chen A, Zagorski B, Parsons D, Vander Laan R. A population based  
302 perspective of acquired brain injury in older adults: How do they happen? *Brain Injury.* 2012;26  
303 (4-5):548-549.
- 304 5. Kerr ZY, Harmon KJ, Marshall SW, Proescholdbell SK, Waller AE. The epidemiology of traumatic  
305 brain injuries treated in emergency departments in North Carolina, 2010-2011. *N C Med J.*  
306 2014;75(1):8-14.
- 307 6. Albrecht JS, Hirshon JM, McCunn M, et al. Increased rates of mild traumatic brain injury among  
308 older adults in US Emergency Departments, 2009-2010. *Journal of Head Trauma Rehabilitation.*  
309 2016;31(5):E1-E7.
- 310 7. Fu WW, Fu TS, Jing R, McFaull SR, Cusimano MD. Predictors of falls and mortality among elderly  
311 adults with traumatic brain injury: A nationwide, population-based study. *PLoS ONE.* 2017;12 (4)  
312 (no pagination)(e0175868).
- 313 8. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe.  
314 *Acta Neurochirurgica.* 2015;157(10):1683-1696.
- 315 9. Hastings DL, Brieding M, Lee R. Falls and traumatic brain injuries in older adults: A worsening  
316 trend. *Journal of the American Geriatrics Society.* 2017;65:S8.
- 317 10. Sung KC, Liang FW, Cheng TJ, Lu TH, Kawachi I. Trends in Unintentional Fall-Related Traumatic  
318 Brain Injury Death Rates in Older Adults in the United States, 1980-2010: A Joinpoint Analysis. *J*  
319 *Neurotrauma.* 2015;32(14):1078-1082.
- 320 11. Fletcher AE, Khalid S, Mallonee S. The epidemiology of severe traumatic brain injury among  
321 persons 65 years of age and older in Oklahoma, 1992-2003. *Brain Injury.* 2007;21(7):691-699.
- 322 12. Chisholm KM, Harruff RC. Elderly deaths due to ground-level falls. *The American journal of*  
323 *forensic medicine and pathology.* 2010;31(4):350-354.

- 1  
2  
3 324 13. Brazinova A, Mauritz W, Majdan M, Rehorcikova V, Leitgeb J. Fatal traumatic brain injury in  
4 325 older adults in Austria 1980-2012: an analysis of 33 years. *Age Ageing*. 2015;44(3):502-506.  
5 326 14. Shankar KN, Liu SW, Ganz DA. Trends and Characteristics of Emergency Department Visits for  
6 327 Fall-Related Injuries in Older Adults, 2003–2010. *Western Journal of Emergency Medicine*.  
7 328 2017;18(5):785-793.  
8 329 15. Hartholt KA, Van Lieshout EM, Polinder S, Panneman MJ, Van der Cammen TJ, Patka P. Rapid  
9 330 increase in hospitalizations resulting from fall-related traumatic head injury in older adults in  
10 331 The Netherlands 1986-2008. *J Neurotrauma*. 2011;28(5):739-744.  
11 332 16. Korhonen N, Niemi S, Parkkari J, Sievanen H, Kannus P. Incidence of fall-related traumatic brain  
12 333 injuries among older Finnish adults between 1970 and 2011. *Jama*. 2013;309(18):1891-1892.  
13 334 17. Verma SK, Willetts JL, Corns HL, Marucci-Wellman HR, Lombardi DA, Courtney TK. Falls and fall-  
14 335 related injuries among community-dwelling adults in the United States. *PLoS ONE*. 2016;11 (3)  
15 336 (no pagination)(e0150939).  
16 337 18. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor  
17 338 head injury. *The Lancet*. 2001;357(9266):1391-1396.  
18 339 19. de Wit K, Merali Z, Kagoma YK, Mercier É. Incidence of intracranial bleeding in seniors  
19 340 presenting to the emergency department after a fall: A systematic review. *Injury*.  
20 341 2020;51(2):157-163.  
21 342 20. Kelen G, Peterson S, Pronovost P. In the Name of Patient Safety, Lets Burden the Emergency  
22 343 Department More. *Annals of Emergency Medicine*.67(6):737-740.  
23 344 21. Émond M, Grenier D, Morin J, et al. Emergency Department Stay Associated Delirium in Older  
24 345 Patients. *Canadian Geriatrics Journal*. 2017;20(1):10-14.  
25 346 22. Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-spine rule for radiography in alert and  
26 347 stable trauma patients. *Jama*. 2001;286(15):1841-1848.  
27 348 23. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without  
28 349 diagnostic imaging: management of patients with suspected pulmonary embolism presenting to  
29 350 the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med*.  
30 351 2001;135(2):98-107.  
31 352 24. Thiruganasambandamoorthy V, Stiell IG, Sivilotti MLA, et al. Risk stratification of adult  
32 353 emergency department syncope patients to predict short-term serious outcomes after discharge  
33 354 (RiSEDS) study. *BMC Emergency Medicine*. 2014;14:8-8.



- 1  
2  
3 355 25. Stiehl IG, Wells GA. Methodologic standards for the development of clinical decision rules in  
4 356 emergency medicine. *Annals of Emergency Medicine*. 1999;33(4):437-447.  
5  
6 357 26. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable  
7 358 prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Annals*  
8 359 of Internal Medicine 2015;162(1):55-63.  
9  
10 360 27. Selvanayagam N, Mowbray F, Clayton N, Soomro A, Varner C, McLeod S, de Wit K.  
11 361 Reliability of patient-reported outcome measures: Hemorrhage, anticoagulant, antiplatelet  
12 362 medication use. 2021;5(4): e12501.  
13  
14 363 28. de Wit K, Parpia S, Varner C, et al. Clinical Predictors of Intracranial Bleeding in Older Adults  
15 364 Who Have Fallen: A Cohort Study. *Journal of the American Geriatrics Society*. 2020;68(5):970-  
16 365 976.  
17  
18 366 29. Schulman S, Kearon C, the SOCOAOTS, Standardization Committee Of The International Society  
19 367 On T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic  
20 368 medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis*.  
21 369 2005;3(4):692-694.  
22  
23 370 30. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly  
24 371 people. *Canadian Medical Association Journal*. 2005;173(5):489-495.  
25  
26 372 31. Lawless JF, Singhal K. Efficient Screening of Nonnormal Regression Models. *Biometrics*.  
27 373 1978;34(2):318-327.  
28  
29 374 32. Harrell F. *Regression Modeling Strategies With Applications to Linear Models, Logistic*  
30 375 *Regression, and Survival Analysis*. Springer New York; 2001.  
31  
32 376 33. Mallett S, Royston P, Dutton S, Waters R, Altman DG. Reporting methods in studies developing  
33 377 prognostic models in cancer: a review. *BMC Medicine*. 2010;8:20.  
34  
35 378 34. Pavlou M, Ambler G, Seaman SR, et al. How to develop a more accurate risk prediction model  
36 379 when there are few events. *BMJ (Clinical research ed)*. 2015;351:h3868.  
37  
38 380 35. PA Harris, R Taylor, R Thielke, J Payne, N Gonzalez, JG. Conde, Research electronic data capture  
39 381 (REDCap). A metadata-driven methodology and workflow process for providing translational  
40 382 research informatics support, *Journal of Biomedical Informatics*. 2009;42(2):377-81.  
41  
42 383 36. PA Harris, R Taylor, BL Minor, V Elliott, M Fernandez, L O'Neal, L McLeod, G Delacqua, F  
43 384 Delacqua, J Kirby, SN Duda, REDCap Consortium, The REDCap consortium: Building an  
44 385 international community of software partners, *Journal of Biomedical Informatics*. 2019,  
45 386 May [doi: 10.1016/j.jbi.2019.103208].

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**Table 1: Description of collected demographic and predictor variables**

|  | Data collected by treating physician at initial assessment | Data collected by medical record review | Comment on predictor choice for rule derivation       |
|--|--|---|---|
| <b>Predictor variables</b>   |  |   |   |
| Age  |  | x                                       | No association found* but will be included            |
| Sex  |  | x                                       | Trend towards association with male sex*              |
| Head injury (as reported by patient or carer)                                | x  |   | Plausible higher risk                                 |
| Loss of consciousness  | x  |   | Marker for head injury severity                       |
| New amnesia about events of fall   | x  |   | Marker for head injury severity                       |
| History of previous major bleed <sup>28</sup>                                |  | x                                       | Trend towards association* and biologically plausible |
| Cirrhosis  |  | x                                       | Biologically plausible                                |
| Previous diagnosis of ischemic stroke  |  | x                                       | Biologically plausible                                |
| Chronic renal impairment   | x  | x                                       | Association demonstrated*                             |
| Reduced Glasgow Coma Score from normal (as indicated by caregiver or family) | x  |   | Association demonstrated*                             |
| Bruise or laceration on the head (any size)                                  | x  |   | Association demonstrated*                             |
| New abnormality on neurological examination                                  | x  |   | Association demonstrated *                            |
| Haemoglobin  |  | x                                       | Biologically plausible                                |
| Platelet count   |  | x                                       | Biologically plausible                                |
| Anticoagulation medication   | x  | x                                       | Commonly held dogma                                   |
| Antiplatelet medication  | x  | x                                       | Commonly held dogma                                   |
| Clinical Frailty Score <sup>30</sup>   | x  |   | Biologically plausible                                |

| <b>Descriptive variables</b>                       |   |   |  |
|--|---|---|--|
| Living circumstances                               |   | x | No association found*  |
| Diabetes   |   | x | No association found*  |
| Hypertension                                       |   | x | No association found*  |
| Active cancer within past 2 years                  |   | x | No association found*  |
| Dementia   |   | x | No association found*  |
| History of frequent falls                          |   | x | Not previously assessed*   |
| Congestive heart failure                           |   | x | No association found*  |
| Mechanism of injury                                |   | x | No association found*  |
| Weight   |   | x | No association found*  |
| Glasgow coma score at time of physician assessment | x |   | Reduced Glasgow Coma Score from normal has a stronger association* |
| Vomiting (once / more than once)                   | x |   | No association found*  |
| Signs of basal skull fracture                      | x |   | Too rare to assess*  |
| Suspected open or depressed skull fracture         | x |   | Too rare to assess*  |
| Retrograde amnesia for >30 minutes                 | x |   | Not previously assessed*   |
| Creatinine   |   | x | No association found*  |
| International normalized ratio (INR)               |   | x | Anticipated missing data   |

\* According to the results of our prior study,<sup>28</sup> N=1753

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