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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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33 **Key words** Older adults, intracranial bleeding, diagnosis, emergency department, clinical decision rules

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3 **34 ABSTRACT**

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5 **35 Introduction**

6
7 36 Falling on level ground is now the most common cause of traumatic intracranial bleeding world-wide.
8
9 37 Older adults frequently present to the emergency department after falling. It can be challenging for
10
11 38 clinicians to determine who requires brain imaging to rule out traumatic intracranial bleeding, and often
12
13 39 head injury decision rules do not apply to older adults who fall. The goal of our study is to derive a
14
15 40 clinical decision rule which will identify older adults who present to the emergency department after a
16
17 41 fall who do not have clinically important intracranial bleeding.

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.
23
24 46 Patients are included if they fall on level ground, off a chair, toilet seat or out of bed. The primary
25
26 47 outcome is the diagnosis of clinically relevant intracranial bleeding within 42 days of the index
27
28 48 emergency department visit. An independent adjudication committee will determine the primary
29
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.
33
34 51 Data extraction is supplemented by an independently structured electronic medical record review. We
35
36 52 will perform binary recursive partitioning using Classification and Regression Trees to derive a clinical
37
38 53 decision rule.

39 **54**
40 **55 Ethics and dissemination**

41 56 The study has been approved by the research ethics boards governing all participating sites. We will
42
43 57 disseminate our results by journal publication, presentation at international meetings and social media.
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45 **58**
46 **59 Registration details** ClinicalTrials.gov NCT03745755
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3 63 **ARTICLE SUMMARY**

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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
10 67 • This study will derive a clinical decision rule to determine which older emergency department
11 patients who present after a fall do not require head CT imaging.
12 68
13 69 • Our clinical decision rule will be composed of routine clinical bedside and laboratory findings.
14
15 70 • The main threat to our study is that not all patients will have head CT imaging at their initial
16 emergency department visit and we will not know if a patient dies of undiagnosed intracranial
17 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 rising¹ and has a worse prognosis.^{2,3} 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.⁴⁻⁸ Fall-associated intracranial bleeding in older adults is increasing in
86 incidence.^{9,10} The mortality rate for fall-associated intracranial bleeding is 15%^{7,11} (accounting for half of
87 all fall-associated deaths^{12,13}). Rather than seeing a decrease in these deaths, this mortality rate is
88 rising.¹⁰ Emergency departments (EDs) are managing an increasing number of older adults who have
89 fallen¹⁴ and ED visits for fall-related head injuries in older adults have increased year after year.^{9,13,15-17}
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.¹⁸
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.¹⁹ 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.²⁰
100 Older adults are at greater risk of developing delirium the longer they stay in the ED.²¹ 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,²²
114 thoracic imaging for pulmonary embolism²³ and admission after syncope.²⁴ Our study follows the
115 methodological standards for clinical decision rules in emergency medicine.²⁵

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.

10 142

11 143 **Outcome definition and measurement**

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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
32
33 154 scans by the centralized outcome adjudication committee consisting of a study neurologist,
34
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)
38
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
45
46 161 intracranial bleeding.²⁶ Furthermore, our experience of personal follow up in this population²⁷ is that it is
47
48 162 frequently not feasible because of residence in nursing homes or baseline cognitive impairment.
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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
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54 165 catchment area.

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56 167 **Predictor variables**

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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 treating physician at initial assessment	Data collected by systematic medical record review by research assistant
Predictor variables		
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 ²⁸		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 ²⁹	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.²⁷ 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 criteria²⁸); 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.²⁹ 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.²⁷

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.^{30,31} 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.^{32,33} We
213 expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,¹⁹ 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.²⁷ 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^{34,35} and stored on a secure server at
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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,²⁷ 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
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35 242 approval to include patients who were unable to give informed consent. It is essential we include
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37 243 patients who cannot consent since they are often the most frail patients who are challenging to evaluate
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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
5 252 The study was conceived by KdW, MM, CK, SS and AW. The protocol was designed with input from
6 253 all authors and has been endorsed by the Network of Canadian Emergency Researchers. The study is
7
8 254 being conducted by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study
9
10 255 adjudicators. SP will oversee the analysis.

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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**

4
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
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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
37
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
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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**

- 6 66 • This cohort study aims to derive a clinical decision rule which identifies older adults at risk of
7 intracranial bleeding after a fall.
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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.
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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 rising¹ and has a worse prognosis.^{2,3} 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.⁴⁻⁸ Fall-associated intracranial bleeding in older adults is increasing in
87 incidence.^{9,10} The mortality rate for fall-associated intracranial bleeding is 15%^{7,11} (accounting for half of
88 all fall-associated deaths^{12,13}). Rather than seeing a decrease in these deaths, this mortality rate is
89 rising.¹⁰ Emergency departments (EDs) are managing an increasing number of older adults who have
90 fallen¹⁴ and ED visits for fall-related head injuries in older adults have increased year after year.^{9,13,15-17}
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.¹⁸
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.¹⁹ 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.²⁰
101 Older adults are at greater risk of developing delirium the longer they stay in the ED.²¹ 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,²²
115 thoracic imaging for pulmonary embolism²³ and admission after syncope.²⁴ Our study follows the
116 methodological standards for clinical decision rules in emergency medicine²⁵ and the Transparent
117 reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.²⁶

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
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5 140 for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if
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7 141 participants return to the ED within 42 days of enrolment with new confusion, headache, loss of
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9 142 balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological
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11 143 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.²⁷ Furthermore, our experience of personal follow up in this population²⁸ 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
20
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
Predictor variables			
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 ²⁸		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 ³⁰	x		Biologically plausible
Descriptive variables			
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*

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3 211 samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed
4 212 versus predicted probabilities.

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7 214 **Sample size**

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9 215 The current guidelines suggest that we would require at least 10 events per included variable.^{33,34} We
10 216 expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,²⁰ and we
11
12 217 assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample
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14 218 size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).
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16 219

17 220 **Sources of bias**

18
19 221 Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is
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21 222 collected before the primary outcome data is collected. However, it is possible that we do not identify
22
23 223 every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of
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25 224 patients had a head CT during the index ED visit.²⁸ Although patients are advised to return if they
26
27 225 develop neurological symptoms, it is possible that a patient may die of an intracranial bleed before
28
29 226 being diagnosed. Furthermore, 42-day follow-up involves institutional electronic medical record review.
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31 227 If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial
32
33 228 bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study
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35 229 enrollment to patients who reside within the hospital catchment area and most sites have access to
36
37 230 records from regional neurosurgical centres. In our prior study where we performed in-person follow
38
39 231 up, no patient was diagnosed with an intracranial bleed at another hospital.

40 232 41 233 **Study oversight**

42 234 The coordinating centre is McMaster University. Electronic data and de-identified source documents are
43
44 235 uploaded to a Research Electronic Data Capture (REDCap) database^{35,36} and stored on a secure server at
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46 236 McMaster University. The coordinating centre validates all data and supervises the adjudication
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48 237 committee activities. The study steering committee consists of the site investigators.

49 238 50 239 **Ethics and dissemination**

51 240 Research ethics approval has been obtained from each enrolling site local research ethics board. In our
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53 241 previous study on the same population,²⁸ we obtained patient consent. An interim analysis showed a
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55 242 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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17 251 The study results will be submitted for publication in a peer reviewed journal and presented at national
18
19 252 and international emergency medicine meetings.

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3 254 **AUTHORS' CONTRIBUTIONS**

4
5 255 The study was conceived by KdW, MM, CK, SP and AW. The protocol was designed with input from
6 256 all authors (KdW, MM, CK, SP, AW, NC, EM, ME, IS, DE, DB, RJ, JM, CV, SM, AP, YK, AS, SS and PE) has
7
8 257 been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted
9
10 258 by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee
11 259 the analysis.

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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**

4
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
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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 43 **Methods and analysis**

19
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
25
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
29
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
37
38 53 decision rule.
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38 55 **Ethics and dissemination**

40 56 The study was initially approved by Hamilton Integrated Research Ethics Committee and subsequently
41
42 57 approved by the research ethics boards governing all participating sites. We will disseminate our results
43
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**

- 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
 - 11 71 independent adjudication committee.
 - 12 72 • The main limitation is that not all patients will have head CT imaging at their initial emergency
 - 13 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 rising¹ and has a worse prognosis.^{2,3} 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.⁴⁻⁸ Fall-associated intracranial bleeding in older adults is increasing in
87 incidence.^{9,10} The mortality rate for fall-associated intracranial bleeding is 15%^{7,11} (accounting for half of
88 all fall-associated deaths^{12,13}). Rather than seeing a decrease in these deaths, this mortality rate is
89 rising.¹⁰ Emergency departments (EDs) are managing an increasing number of older adults who have
90 fallen¹⁴ and ED visits for fall-related head injuries in older adults have increased year after year.^{9,13,15-17}
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.¹⁸
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.¹⁹ 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.²⁰
101 Older adults are at greater risk of developing delirium the longer they stay in the ED.²¹ 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,²²
115 thoracic imaging for pulmonary embolism²³ and admission after syncope.²⁴ Our study follows the
116 methodological standards for clinical decision rules in emergency medicine²⁵ and the Transparent
117 reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.²⁶

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
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5 140 for CT, hospitals have limited resources and ordering a CT delays discharge home. However, if
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7 141 participants return to the ED within 42 days of enrolment with new confusion, headache, loss of
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9 142 balance, repeat falls, change in behaviour, reduced Glasgow Coma Score (GCS) or other neurological
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11 143 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.²⁷ Furthermore, our experience of personal follow up in this population²⁸ 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
16
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
20
21 **180** demographic and predictor variables collected.
22

23 **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
Predictor variables			
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 ²⁸		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 ³⁰	x		Biologically plausible
Descriptive variables			
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*

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3 211 samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed
4 212 versus predicted probabilities.

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7 214 **Sample size**

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9 215 The current guidelines suggest that we would require at least 10 events per included variable.^{33,34} We
10 216 expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,²⁰ and we
11 217 assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample
12 218 size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).

13
14 219

15 220 **Sources of bias**

16 221 Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is
17 222 collected before the primary outcome data is collected. However, it is possible that we do not identify
18 223 every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of
19 224 patients had a head CT during the index ED visit.²⁸ Although patients are advised to return if they
20 225 develop neurological symptoms, it is possible that a patient may die of an intracranial bleed before
21 226 being diagnosed. Furthermore, 42-day follow-up involves institutional electronic medical record review.
22 227 If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial
23 228 bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study
24 229 enrollment to patients who reside within the hospital catchment area and most sites have access to
25 230 records from regional neurosurgical centres. In our prior study where we performed in-person follow
26 231 up, no patient was diagnosed with an intracranial bleed at another hospital.

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28 232

29 233 **Study oversight**

30 234 The coordinating centre is McMaster University. Electronic data and de-identified source documents are
31 235 uploaded to a Research Electronic Data Capture (REDCap) database^{35,36} and stored on a secure server at
32 236 McMaster University. The coordinating centre validates all data and supervises the adjudication
33 237 committee activities. The study steering committee consists of the site investigators.

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36 239 **Ethics and dissemination**

37 240 Research ethics approval has been obtained from each enrolling site local research ethics board. In our
38 241 previous study on the same population,²⁸ we obtained patient consent. An interim analysis showed a
39 242 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
12
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.

16 250

17 251 The study results will be submitted for publication in a peer reviewed journal and presented at national
18
19 252 and international emergency medicine meetings.

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3 254 **AUTHORS' CONTRIBUTIONS**

4
5 255 The study was conceived by KdW, MM, CK, SP and AW. The protocol was designed with input from
6 256 all authors (KdW, MM, CK, SP, AW, NC, EM, ME, IS, DE, DB, RJ, JM, CV, SM, AP, YK, AS, SS and PE) has
7
8 257 been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted
9
10 258 by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee
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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**

4
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.
23
24 46 Patients are included if they fall on level ground, off a chair, toilet seat or out of bed. The primary
25
26 47 outcome is the diagnosis of clinically relevant intracranial bleeding within 42 days of the index
27
28 48 emergency department visit. An independent adjudication committee will determine the primary
29
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
37
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
45
46 58 by journal publication, presentation at international meetings and social media.
47

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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 • This cohort study aims to derive a clinical decision rule which identifies older adults at risk of
7 intracranial bleeding after a fall.
8 67
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 rising¹ and has a worse prognosis.^{2,3} 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.⁴⁻⁸ Fall-associated intracranial bleeding in older adults is increasing in
87 incidence.^{9,10} The mortality rate for fall-associated intracranial bleeding is 15%^{7,11} (accounting for half of
88 all fall-associated deaths^{12,13}). Rather than seeing a decrease in these deaths, this mortality rate is
89 rising.¹⁰ Emergency departments (EDs) are managing an increasing number of older adults who have
90 fallen¹⁴ and ED visits for fall-related head injuries in older adults have increased year after year.^{9,13,15-17}
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.¹⁸
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.¹⁹ 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.²⁰
101 Older adults are at greater risk of developing delirium the longer they stay in the ED.²¹ 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,²²
115 thoracic imaging for pulmonary embolism²³ and admission after syncope.²⁴ Our study follows the
116 methodological standards for clinical decision rules in emergency medicine²⁵ and the Transparent
117 reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.²⁶

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

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8 141 **Patient assessment**

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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
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22 148 symptoms, they will undergo head CT.

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25 150 **Outcome definition and measurement**

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27 151 The primary outcome is '***clinically important intracranial bleeding***' diagnosed within 42 days of the
28
29 152 index ED presentation. Our definition was derived after surveying specialists (including neurosurgeons,
30
31 153 neurologists, trauma physicians, geriatricians, thrombosis and emergency physicians) who determined
32
33 154 that symptoms from intracranial bleeding might develop as late as six weeks after a fall. 'Clinically
34
35 155 important intracranial bleeding' is defined as bleeding within the cranial vault (including subdural,
36
37 156 intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires
38
39 157 medical or surgical treatment. Medical treatment is defined as any of the following: temporary or
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41 158 permanent discontinuation of anticoagulant or antiplatelet medication; administration of an
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43 159 antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation.
44
45 160 Clinically important intracranial bleeding will be determined by independent adjudication of head CT
46
47 161 scans by the centralized outcome adjudication committee consisting of a study neurologist,
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49 162 neurosurgeon, trauma surgeon and radiologist. The adjudicators will be blinded to all ED baseline data.
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51 163 Each scan will be adjudicated independently by two reviewers. In the case of a disagreement, a third
52
53 164 adjudicator, blinded to the prior reviews, will determine the classification. Agreement between the
54
55 165 adjudicators will be reported. Secondary outcomes relate to the 'severity' of the intracranial bleeding: 1)
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57 166 neurosurgical intervention; 2) intensive care admission; 3) hospital length of stay; 4) in-hospital death as
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59 167 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
4
5 170 intracranial bleeding.²⁷ Furthermore, our experience of personal follow up in this population²⁸ is that it is
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7 171 frequently not feasible because of residence in nursing homes or baseline cognitive impairment.
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9 172 Therefore, the current study follow up is restricted to systematic medical record review with
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11 173 independent validation and enrollment is restricted to patients who reside within the hospital
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13 174 catchment area.

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15 176 **Predictor variables**

16
17 177 Demographic and predictor variables are collected in two ways: 1) the treating physician completes a
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19 178 standardized data collection form at the time of initial patient assessment, and before the results of the
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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
30
31 184 site investigator resolves discrepancies which persist after research assistant review. Table 1 details the
32
33 185 demographic and predictor variables collected.

32 186

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.²⁸ We selected 17 candidate predictor
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40 190 variables, which are considered to be biologically plausible and related to the outcome of intracranial
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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 criteria²⁹);
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46 193 cirrhosis; prior ischemic stroke; chronic renal impairment; GCS reduced from baseline; bruise or
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48 194 laceration on the head; abnormal neurological examination; haemoglobin, platelet count; anticoagulant
49
50 195 therapy; antiplatelet therapy; and, Clinical Frailty Score.³⁰

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

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2
3 201 develop a decision rule. A clinical decision rule for a life-threatening event like intracranial bleeding
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5 202 requires very high sensitivity. The model with a sensitivity of > 99% and the highest specificity will be
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7 203 selected. We will assess the derived decision rule by comparing the classification of each patient with his
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9 204 or her actual status for the primary outcomes. In addition, 1000 bootstrap iterations will be performed
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11 205 to assess the internal classification performance and overfitting of the selected decision rule.
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13 206
14 207 We will also develop a predictive risk model using multivariable logistic regression. Continuous variables
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16 208 may be transformed and will be fit using restricted cubic splines to relax the linearity assumption. First, a
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18 209 full model with all variables will be fit. To further reduce the model, we will perform backward
19
20 210 elimination without model re-fitting with $p < 0.5$, which has shown to have valid inference.^{31,32} Clinically
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22 211 and biologically plausible interactions will be tested within the model. Internal validation to obtain
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24 212 unbiased and optimism corrected estimation of model performance will be done using 1000 bootstrap
25
26 213 samples. Model discrimination will be reported using the C-statistic and a calibration plot of observed
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28 214 versus predicted probabilities.
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30 215
31 216 **Sample size**
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33 217 The current guidelines suggest that we would require at least 10 events per included variable.^{33,34} We
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35 218 expect that 5% of patients will be diagnosed with clinically important intracranial bleeding,²⁰ and we
36
37 219 assume that our initial model will consist of 17 candidate variables. Based on this assumption, a sample
38
39 220 size of 4000 should include 200 cases of intracranial bleeding (12 events per variable).
40

41 221
42 222 **Sources of bias**
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44 223 Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is
45
46 224 collected before the primary outcome data is collected. However, it is possible that we do not identify
47
48 225 every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of
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50 226 patients had a head CT during the index ED visit and 6/738 participants without a head CT (0.8%) were
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52 227 subsequently diagnosed with intracranial bleeding within 42 days.²⁸ In comparison, 6/939 (0.6%) with a
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54 228 negative head CT were diagnosed with intracranial bleeding within 42 days, suggesting emergency
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56 229 physicians may correctly identify lower risk patients who do not require a scan. However, this evidence
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58 230 is indirect and hypothesis generating only. Given that not all participants in this study will have a head
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60 231 CT scan at baseline, we may underdiagnose intracranial bleeding in this subpopulation which will
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233 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
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5 234 without testing for intracranial bleeding. Furthermore, 42-day follow-up involves institutional electronic
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7 235 medical record review. If a patient attended an unrelated hospital during follow up and was diagnosed
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9 236 with an intracranial bleed, we might miss this diagnosis. To reduce the chance of this happening, we are
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11 237 restricting study enrollment to patients who reside within the hospital catchment area and most sites
12
13 238 have access to records from regional neurosurgical centres. In our prior study where we performed in-
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15 239 person follow up, no patient was diagnosed with an intracranial bleed at another hospital. The imperfect
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17 240 reference standard bias introduced with differential testing depending on the emergency physician CT
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19 241 request, might inflate the strength of association between predictor variables which are commonly
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21 242 utilized to determine the need for head CT in this population (such as a history of loss of consciousness
22
23 243 and anticoagulation use).

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245 **Study oversight**

246 The coordinating centre is McMaster University. Electronic data and de-identified source documents are
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248 uploaded to a Research Electronic Data Capture (REDCap) database^{35,36} and stored on a secure server at
249
250 McMaster University. The coordinating centre validates all data and supervises the adjudication
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252 committee activities. The study steering committee consists of the site investigators.

253

254 **Ethics and dissemination**

255 Research ethics approval has been obtained from each enrolling site local research ethics board. In our
256
257 previous study on the same population,²⁸ we obtained patient consent. An interim analysis showed a
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259 number of patients were confused (144/890, 16%) or died before a researcher could ask for their
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261 consent (39/890, 4%). Family were often not available in the ED. In all, we were unable to obtain
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263 consent from 204/890 (23%) patients. To address this problem, we obtained research ethics board
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265 approval to include patients who were unable to give informed consent. It is essential we include
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267 patients who cannot consent since they are often the most frail patients who are challenging to evaluate
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269 in the ED and frequently excluded from studies. Excluding these patients could limit the generalizability
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271 of our clinical decision rule. The current study has research ethics approval at all sites to include patients
272
273 without obtaining informed consent.

274

275 The study results will be submitted for publication in a peer reviewed journal and presented at national
276
277 and international emergency medicine meetings.

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3 265 **AUTHORS' CONTRIBUTIONS**

4
5 266 The study was conceived by KdW, MM, CK, SP and AW. The protocol was designed with input from
6 267 all authors (KdW, MM, CK, SP, AW, NC, EM, ME, IS, DE, DB, RJ, JM, CV, SM, AP, YK, AS, SS and PE) has
7
8 268 been endorsed by the Network of Canadian Emergency Researchers. The study is being conducted
9
10 269 by KdW, NC, EM, CV, DE, DB, RJ and JM. YK, AS, SS and PE are the study adjudicators. SP will oversee
11 270 the analysis.
12

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14
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20 275
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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
Predictor variables			
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 ²⁸		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 ³⁰	x		Biologically plausible

Descriptive variables			
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

388 * According to the results of our prior study,²⁸ N=1753

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