

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	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.
<b>AUTHORS</b>	de Wit, Kerstin; Mercuri, Mathew; Clayton, Natasha; Worster, Andrew; Mercier, Eric; Emond, Marcel; Varner, Catherine; McLeod, Shelley; Eagles, Debra; Stiell, Ian; Barbic, David; Morris, Judy; Jeanmonod, Rebecca; Kagoma, Yoan; Shoamanesh, Ashkan; Engels, Paul; Sharma, Sunjay; Kearon, Clive; Papaioannou, Alexandra; Parpia, Sameer

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Kosuke Mori Yokohama Municipal Citizens Hospital, Emergency Medicine
<b>REVIEW RETURNED</b>	20-Oct-2020

<b>GENERAL COMMENTS</b>	<p>I reviewed your study protocol with great interest. I agree that as the population ages, there will be an increase in the number of elderly patients presenting to the emergency room with the primary complaint of head trauma from falls, leading to cost and ED crowding issues. So it would be useful to develop a rule to stratify low-risk patients without intracranial injury among older patients injured by ground-level falls. However, I have some concerns regarding the definition of primary outcomes and how to follow up with patients who return home.</p> <p>The indications for a change in medical treatment are unclear, and there are concerns about its reproducibility. I think that the treatment for head trauma is determined not only by imaging findings but also by clinical findings, and therefore it may be inappropriate for treatment to be determined solely by head CT findings independent of clinical findings.</p> <p>I consider it inadequate that the 40% of patients who do not have a CT are followed up by chart review alone. I think we cannot rule out the possibility that the 40% of patients who did not have a CT taken at their index ED visit, even if they did not visit the hospital during the subsequent 6 weeks, would have an intracranial injury that would meet the indications for a change in medical treatment.</p>
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<b>REVIEWER</b>	Phichayut Phinyo Chiang Mai University, Center for clinical epidemiol
<b>REVIEW RETURNED</b>	20-Oct-2020

<b>GENERAL COMMENTS</b>	This excellent and comprehensive study protocols explain detailed steps on how to derive a clinical decision rule for emergency department head CT scanning in older adults who have fallen. I would like to praise all the investigators for such great work on the drafting of the protocol. The design planning is well standardized
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	<p>and appropriate. However, I do have some concerns regarding the clarity of some predictors and statistical analysis.</p> <ul style="list-style-type: none"> <li>- I suggests the authors to (also) follow the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement in reporting of the methodological design. ( page 8 line 115)</li> <li>- You have misspelled 'Glasgow Coma Score" in Table 1, please correct this point or use abbreviated version, GCS, as in GCS at time of physician assessment.</li> <li>- Although 'reduced GCS from normal' and 'bruise or laceration on the head' have been previously identified as significant predictors in your previous work, a clearer definition of both predictors should be improved or clarified in the study protocol. For instance, how do physicians define normal GCS in each patients?, by asking their families or search through recent medical records? what's the character of bruising and laceration that should be considered as significant? would very small bruise count? or all wounds should be counted regardless of their sizes?</li> <li>- The authors have stated that they have selected 17 candidate predictors from a list of initially identified potential predictors from literature. Suspected open or depressed skull fractures, retrograde amnesia were excluded due to their rarity in practice. However, some predictors were missed from the list of candidate without specifying reasons such as vomiting, cancer treated within the past 2 years. It might be more informative to specify the reason of inclusion and exclusion by adding another column to Table 1.</li> <li>-Regarding multivariable logistic modeling, the authors stated that backward selection without model refitting would be use at a p-value cut point &lt;0.5. I suggest that the term should be change to backward elimination rather than backward selection, and please check if the cut point of less than 0.5 is correct. I understand that the relaxation of p-value is important to prevent model overfitting, however using p-value&lt;0.5 might not be appropriate. Moreover, in case that you already have estimated sample size that would be adequate for all 17 predictors, I see no reason to specify model reduction approach.</li> <li>- Recently, a new calculating approach for sample size of developing a clinical prediction model was published in BMJ 2020 (<a href="https://www.bmj.com/content/368/bmj.m441">https://www.bmj.com/content/368/bmj.m441</a>). If possible, I suggest the authors to imply this novel approach to further strengthen the study protocol.</li> </ul>
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**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Dr. Kosuke Mori, Yokohama Municipal Citizens Hospital, Yokohama City University Medical Center

Comments to the Author:

I reviewed your study protocol with great interest. I agree that as the population ages, there will be an increase in the number of elderly patients presenting to the emergency room with the primary complaint of head trauma from falls, leading to cost and ED crowding issues. So it would be useful to develop a rule to stratify low-risk patients without intracranial injury among older patients injured by

ground-level falls. However, I have some concerns regarding the definition of primary outcomes and how to follow up with patients who return home.

- The indications for a change in medical treatment are unclear, and there are concerns about its reproducibility. I think that the treatment for head trauma is determined not only by imaging findings but also by clinical findings, and therefore it may be inappropriate for treatment to be determined solely by head CT findings independent of clinical findings.

• Thank you for raising this point. Our primary outcome is 'clinically important intracranial bleeding'. We also agree that an abnormal head CT scan does not necessarily relate to an important finding. Since we are deriving a clinical decision rule for detecting intracranial bleeding (as opposed to a prognostic rule), it is vital that our definition of clinically important intracranial bleeding includes all cases of intracranial bleeding which require treatment, including cessation of anticoagulation, reversal of anticoagulation, hospital neuro-observation and neurosurgery.

Our prior study (<https://agsjournals.onlinelibrary.wiley.com/doi/abs/10.1111/jgs.16338>) showed that 12/88 patients diagnosed with intracranial bleeding on head CT were discharged home without further complication. Of the 63/88 patients with intracranial bleeding who were admitted to a regular hospital ward without undergoing neurosurgery, 15 died, demonstrating that older adults are not always offered surgery for serious traumatic brain injury, or else sometimes they decline surgery. We cannot, therefore, restrict the definition of clinically important intracranial bleeding to those who require intensive care therapy, neurosurgery or die, as is customary for younger patient cohorts. Furthermore, using the modified Rankin scale would also not be appropriate since this is a measure of functional recovery after treatment. Therefore, our definition of clinically important intracranial bleeding is 'bleeding within the cranial vault (including subdural, intracerebral, intraventricular, subarachnoid, epidural blood and cerebral contusion), which requires medical or surgical treatment. Medical treatment is defined as any of the following: temporary or permanent discontinuation of anticoagulant or antiplatelet medication; administration of an antifibrinolytic drug; reversal of anticoagulation; or admission to hospital for neurological observation.'

Treatment of intracranial bleeding is left to treating physicians who take into consideration all clinical information. In Canada and America, treatment guidance is provided by neurosurgery and there are no guidelines for medical or surgical treatment of these patients.

- I consider it inadequate that the 40% of patients who do not have a CT are followed up by chart review alone. I think we cannot rule out the possibility that the 40% of patients who did not have a CT taken at their index ED visit, even if they did not visit the hospital during the subsequent 6 weeks, would have an intracranial injury that would meet the indications for a change in medical treatment.

• You are correct, that we cannot completely rule out the possibility that those patients who do not have a head CT do not have intracranial bleeding. However, if these patients re-present to hospital with neurological symptoms or signs, they will undergo head CT, in the same way that those who have an initial negative head CT will. We have clearly stated this in our limitations section. It would not be possible to perform a head CT on every patient. There is no indication for head CT for many of these patients. The logistics and costs for performing a head CT on all patients while they are in the emergency department would render our study impossible. We chose not to restrict the sample to those who have a head CT in the emergency department since this would introduce spectrum bias. Based on our prior study, our follow up is restricted to chart review for several reasons. Firstly, we require patient consent to call participants in follow up. Requiring consent then further restricts the study to those with capacity to give consent. In our first study, 27% of patients had dementia and many more delirium. We would not be able to include these patients if consent is required since we were seldom able to speak with a relative or next of kin in our previous study. Secondly, follow up communication by telephone was quite challenging for our study since some older adults have reduced hearing or communication problems, and some moved into long term care where it is not possible to speak by telephone with the patient. Lastly, but most importantly, we found the data we

recorded with telephone follow up was at times incorrect. For example, 2/3 patients who had intracranial bleeding denied having had this health problem and other participants claimed wrongly they had had intracranial bleeding. To summarize, telephone follow up would introduce further spectrum bias, is logistically challenging and did not alert our research team to any intracranial bleeding event that we had not already identified by chart review. Although in-person follow up seems at first to be the best approach, in this particular patient cohort, it will introduce spectrum bias, will almost certainly not be possible for a sizeable proportion of patients and may introduce misclassification of the primary outcome.

Reviewer: 2

Dr. Phichayut Phinyo, Chiang Mai University

Comments to the Author:

- This excellent and comprehensive study protocols explain detailed steps on how to derive a clinical decision rule for emergency department head CT scanning in older adults who have fallen. I would like to praise all the investigators for such great work on the drafting of the protocol. The design planning is well standardized and appropriate. However, I do have some concerns regarding the clarity of some predictors and statistical analysis.

- I suggests the authors to (also) follow the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement in reporting of the methodological design. ( page 8 line 115)

- Thank you for pointing this out. We have reviewed the TRIPOD checklist to be sure we included all the relevant information in this manuscript and we have added the TRIPOD reference.

- You have misspelled 'Glasgow Coma Score" in Table 1, please correct this point or use abbreviated version, GCS, as in GCS at time of physician assessment.

- Thank you for pointing this out. We have changed to 'Glasgow coma score' for both.

- Although 'reduced GCS from normal' and 'bruise or laceration on the head' have been previously identified as significant predictors in your previous work, a clearer definition of both predictors should be improved or clarified in the study protocol. For instance, how do physicians define normal GCS in each patients?, by asking their families or search through recent medical records? what's the character of bruising and laceration that should be considered as significant? would very small bruise count? or all wounds should be counted regardless of their sizes?

- When a patient's GCS is less than 15, emergency physicians verify usual GCS by talking with family or else a caregiver (for example to elucidate whether confusion is new). We ask emergency physicians to record the presence of any bruise or laceration on the head, regardless of size. We have added these clarifications to Table 1.

- The authors have stated that they have selected 17 candidate predictors from a list of initially identified potential predictors from literature. Suspected open or depressed skull fractures, retrograde amnesia were excluded due to their rarity in practice. However, some predictors were missed from the list of candidate without specifying reasons such as vomiting, cancer treated within the past 2 years. It might be more informative to specify the reason of inclusion and exclusion by adding another column to Table 1.

- Thank you. We have added a fourth column to Table 1 which explains why a variable was chosen for clinical decision rule derivation or not.

-Regarding multivariable logistic modeling, the authors stated that backward selection without model refitting would be use at a p-value cut point <0.5. I suggest that the term should be change to

backward elimination rather than backward selection, and please check if the cut point of less than 0.5 is correct. I understand that the relaxation of p-value is important to prevent model overfitting, however using p-value<0.5 might not be appropriate. Moreover, in case that you already have estimated sample size that would be adequate for all 17 predictors, I see no reason to specify model reduction approach.

- Our primary analysis will use Classification and Regression Trees (CART) to derive a decision rule. Our secondary analysis will develop a predictive risk model. As suggested, we have changed 'backward selection' to 'backward elimination'. Our sample size was based on all 17 candidate predictors, but model reduction has been proposed to obtain a more parsimonious model.

- Recently, a new calculating approach for sample size of developing a clinical prediction model was published in BMJ 2020 (<https://www.bmj.com/content/368/bmj.m441>). If possible, I suggest the authors to imply this novel approach to further strengthen the study protocol.

- Thank you for suggesting this sample size calculation. However, our primary analysis will use CART to produce a clinical decision rule rather than a prediction rule. This sample size analysis was not available to our team when we proposed the study and the study has been recruiting for almost two years. The sample size is already set and practical issues such as per patient funding would prevent us from changing our sample size. In this instance we will not be able to re-calculate our sample size, however we look forward to using this approach for future clinical prediction studies.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Kosuke Mori Yokohama Municipal Citizens Hospital, Emergency Medicine
<b>REVIEW RETURNED</b>	08-Feb-2021

<b>GENERAL COMMENTS</b>	<p>I am very interested in research on emergency medical care for the elderly and minor head trauma. And I think it is an important topic.</p> <p>I think primary outcomes are unclear. It is important to define the indications for discontinuation of anticoagulant or antiplatelet medication and administration of an antifibrinolytic drug. If the indications are determined by imaging findings rather than clinical findings, it is problematic that only 60% of patients undergo CT.</p>
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<b>REVIEWER</b>	Phichayut Phinyo Chiang Mai University, Center for clinical epidemiology and clinical statistics, Faculty of Medicine
<b>REVIEW RETURNED</b>	30-Jan-2021

<b>GENERAL COMMENTS</b>	The authors have done a good job responding to all my concerns. I suggest this protocol be published in its current form.
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#### VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Kosuke Mori, Yokohama Municipal Citizens Hospital, Yokohama City University Medical Center

Comments to the Author:

I am very interested in research on emergency medical care for the elderly and minor head trauma. And I think it is an important topic.

I think primary outcomes are unclear. It is important to define the indications for discontinuation of anticoagulant or antiplatelet medication and administration of an antifibrinolytic drug. If the indications are determined by imaging findings rather than clinical findings, it is problematic that only 60% of patients undergo CT.

Response:

Thank you for this feedback. In this study, the decision to hold an anticoagulant or antiplatelet agent, to administer anticoagulation reversal or antifibrinolytic therapy is made by the treating physician, with advice from a neurosurgeon. The decision is based on all clinical information and not based solely on the CT scan findings. Our study does not intervene on treatment of intracranial bleeding because: 1). There are no North American guidelines on optimal therapy for intracranial bleeding and 2). This is an observational study with waived consent.

Clearly, patients who do not undergo head CT are not diagnosed with intracranial bleeding. Without a head CT there would be no indication to hold medications, administer reversal or antifibrinolytic agent.

Please also see our prior answer to this point

• ‘You are correct, that we cannot completely rule out the possibility that those patients who do not have a head CT do not have intracranial bleeding. However, if these patients re-present to hospital with neurological symptoms or signs, they will undergo head CT, in the same way that those who have an initial negative head CT will. We have clearly stated this in our limitations section. It would not be possible to perform a head CT on every patient. There is no indication for head CT for many of these patients. The logistics and costs for performing a head CT on all patients while they are in the emergency department would render our study impossible. We chose not to restrict the sample to those who have a head CT in the emergency department since this would introduce spectrum bias.’

Please also be aware that since we submitted this manuscript for consideration of publication in BMJ Open in September 2020, this study completed recruitment, therefore we are not able to change our protocol.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Kosuke Mori Yokohama Municipal Citizens Hospital, Emergency Medicine
<b>REVIEW RETURNED</b>	11-May-2021
<b>GENERAL COMMENTS</b>	I think it is a very interesting and important topic, and I'm looking forward to the results. I have two requests for your paper. The first is a discussion of the group of patients who did not undergo CT at their first ED visit. I think that this discussion should include whether the group of patients who did not have CT scans can truly be considered low risk. Second, it should state how many adjudicators will make the decision about clinically important intracranial bleeding, and the $\kappa$ value.

## VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Dr. Kosuke Mori, Yokohama Municipal Citizens Hospital, Yokohama City University Medical Center  
Comments to the Author:

I think it is a very interesting and important topic, and I'm looking forward to the results. I have two requests for your paper. The first is a discussion of the group of patients who did not undergo CT at their first ED visit. I think that this discussion should include whether the group of patients who did not have CT scans can truly be considered low risk.

- This is a fair point. We have edited page 11 under 'Sources of bias' which now reads:

'Intracranial bleeding will be adjudicated blind to all baseline and predictor data. Predictor data is collected before the primary outcome data is collected. However, it is possible that we do not identify every case of intracranial bleeding during the 42-day follow up period. In our prior study, only 60% of patients had a head CT during the index ED visit and 6/738 participants without a head CT (0.8%) were subsequently diagnosed with intracranial bleeding within 42 days.<sup>28</sup> In comparison, 6/939 (0.6%) with a negative head CT were diagnosed with intracranial bleeding within 42 days, suggesting emergency physicians may correctly identify lower risk patients who do not require a scan. However, this evidence is indirect and hypothesis generating only. Given that not all participants in this study will have a head CT scan at baseline, we may underdiagnose intracranial bleeding in this subpopulation which will comprise around 40% of the cohort. Although patients are advised to return if they develop neurological symptoms, it is possible that a patient may die of an intracranial bleed or else fully recover without testing for intracranial bleeding. Furthermore, 42-day follow-up involves institutional electronic medical record review. If a patient attended an unrelated hospital during follow up and was diagnosed with an intracranial bleed, we might miss this diagnosis. To reduce the chance of this happening, we are restricting study enrollment to patients who reside within the hospital catchment area and most sites have access to records from regional neurosurgical centres. In our prior study where we performed in-person follow up, no patient was diagnosed with an intracranial bleed at another hospital. The imperfect reference standard bias introduced with differential testing depending on the emergency physician CT request, might inflate the strength of association between predictor variables which are commonly utilized to determine the need for head CT in this population (such as a history of loss of consciousness and anticoagulation use).'

Second, it should state how many adjudicators will make the decision about clinically important intracranial bleeding, and the  $\kappa$  value.

- Thank you. This has been added to page 7 under title 'Outcome definition and measurement'.