PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Developing a machine learning algorithm to predict probability of retear and functional outcomes in patients undergoing rotator cuff repair surgery: protocol for a retrospective, multicenter study
AUTHORS	Allaart, Laurens; Spanning, Sanne; Lafosse, Laurent; Lafosse, Thibault; Ladermann, Alexandre; Athwal, George; Hendrickx, Laurent; Doornberg, Job; van den Bekerom, M.P.J.; Buijze, Geert Alexander

VERSION 1 – REVIEW

REVIEWER	DE HOLANDA, LEDYCNARF Universidade Federal do Rio Grande do Norte, Fisioterapia
REVIEW RETURNED	01-Jun-2022

| GENERAL COMMENTS | Dear authors,

Congratulations on the development of a new machine learning (ML) algorithm of great relevance for rotator cuff repair surgery and ML algorithm developers.

This manuscript outlines a protocol for a retrospective multicenter cohort study to develop and train an algorithm that can be used as an online available clinical prediction tool, to predict the risk of retear in patients undergoing rotator cuff repair. They propose to explore any datasets including at least 1000 patients.

This protocol can be useful for other similar research in the field of health professionals and algorithms developers. From this point of view, all this information should be clear in the whole manuscript, which I will describe below.

The methods section in the abstract needs to insert the name of each algorithm development step, and inform which metrics will be used to evaluate the algorithm.

ML and artificial intelligence (AI) algorithms have been implemented to favor prediction and diagnosis of disease and support therapeutic decision making. From this perspective, how can this support your study? What gaps from previous studies will your research fill? I strongly suggest that all this information be in the introduction section.

In the methods section, they should elaborately create a figure to summarize all the steps of algorithm development. Furthermore, I feel this section needs more information about what information about clinical examination findings should be considered as criteria? (1) what will be the algorithm labels? (2) what will be the |

features extractions? (3) how will they manage with missing data? (4) how will the statistical analysis be done? (5)

The discussion section of the paper lacks technicality and highlights its high contribution.

Yours sincerely,
Reviewer

REVIEWER	van Noort, A Spaarne Gasthuis, Orthopedic surgery
REVIEW RETURNED	18-Jun-2022

GENERAL COMMENTS	Compliments to the authors for this very interesting and really important study. To my opinion there only are only a few, nevertheless important, questions to be answered. In developing and training a machine learning algorithm it's offcourse essential to incorporate as much portentially influential factors as possible. Taking supplemental 2 into mind I miss patient related factors like: 1. Psychological factors eg: a medical history of depression, anxiety . Symptoms of catastrophic behaviour. A medical history of difficult objectifiable disorders like fibromyalgia. 2. Sports activity (level) 3. Work related factors: Workers compensation (yes/no) has been described as an important factor related to outcome after rotator cuff surgery. I'm looking forard to receive the comments of the authors Regards

REVIEWER	Pierami, Rafael instituto israelita de ensino e pesquisa do Hospital Albert Einstein, Sistema Locomotor
REVIEW RETURNED	16-Sep-2022

GENERAL COMMENTS	Thank you for inviting me to review this protocol. The authors have made a significant effort, planning, developing and presenting their study protocol. I wish them well with the conduct of their study and look forward to the results. 1. Title: The authors report the protocol for a retrospective multicenter cohort study that aims to develop a clinical prediction tool to predict the retear risk in patients undergoing rotator cuff repair. However, since the primary outcomes defined were retear rate and enduring clinical outcomes, it seems to me that the study is covering more than just the retear rate probability. I would recommend that the functional outcome (enduring clinical outcomes) should be included in the title of the study. 2. Line 70 - On the first paragraph, the first reference (1) is dated from 2004; I would suggest that the authors replace it or add new data 3. Line 75- "Multiple leaders in shoulder surgery" seems to be a little vague in my opinion. I would recommend the authors to rephrase it.

4. Line 77- It is established that worker's compensation claim is associated with poorer patient reported outcomes. I would suggest the authors to add this to the study protocol

5. Line 79- the paragraph: "However, a majority… pathology-specific grading" denotes a less value feeling over these "daunted surgeons"; these surgeons are actually basing their practices on the available and recommended data. I would suggest the authors to rephrase the sentence

6. Line 86- the references (9) and (11) are dated form 1992 and 2000; I would suggest the authors to add newer data

7. Lines 91 to 94 – the study seems to encompass retear-chance and also the clinical improvement-chance. I would suggest that the authors add this information in this section

8. Line 101- the authors did not define the time period in which they performed the systematic literature search. Since there was a significant evolution on the techniques and materials, it seems that this timeframe is important.

9. Line 108- the author performed the systematic search only on PubMed. Why not include other databases, such Scopus, EMBASE and Web of Science?

10. Line 109- The population of 1.000 patients seems to be large enough to address the question of the study. However, it is based on some statistical analysis? I would suggest the authors to be more specific on this issue

11. Line 113- The authors should explain how the randomization process will be or was performed

12. Line 117- the Sugaya's classification for rotator cuff retear is not dichotomous. So, I would suggest the authors to be more specific on this subject

13. Line 123- All the primary and secondary outcomes are categorical; so this information is not necessary

14. Line 148- It seems to me that the algorithm, after all, will predict the patients with retear of rotator cuff AND unsatisfactory functional outcomes and not only patients with rotator cuff retear. I would suggest the author to be more clear and specific about this.

15. Line 157- Ethics and Dissemination: the authors should explain whether they will make and how they will make the data obtained public

16. Line 171 and 172- The authors cite a recent meta-analysis however they did not mention or reference any. Please add the reference for this citation

17. Line 173 and 174- On the study conducted by Carbonel et. Al (21) the conclusion was that the clinical outcomes in patients with a partial thickness tear is similar to those with intact repair. The authors suggests that in patients with full thickness retear "there

	does appear to be a greater clinical and funciotnal impact". I would suggest the editor to advise the authors to rephrase this sentence.
	18. Line 185- I would suggest the authors to replace the word profit to benefit or similar
	19. Lines 186 to 187- as previously said, the study seems to be covering more than the retear rate alone. I would suggest the authors to add the information that, after all, the algorithm will also predict the chance of a non enduring clinical outcome
	20. Line 189- in my opinion, the fact that this is a multicenter study is a strength of the study. If any variance on variables or missing data is noted, it should be elucidated on the results sections of the final paper

REVIEWER	Craig, Richard University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
REVIEW RETURNED	17-Sep-2022

| GENERAL COMMENTS | Thank you for sharing this protocol. This seems to be a well thought out study concept. I would be grateful for some clarifications, particularly in the methods section.

- It took some time to understand that this study will be using individual participant data from existing studies. Please make this more explicit in the collecting data section.
- Whilst I recognise that this study is ongoing, please try to keep the tense of the writing consistent as it describes a piece of future work
- In the machine learning section - this needs expert statistical review.
- Is an 80:20 split the most efficient use of the data? Have bootstrapping methods been considered?
- I am unfamiliar with the Felsch reference. Please expand the text here to speed out what complications you will be recording and how to grade them
- External validation - this needs to be properly described. Has an external validation study been planned? Where will the data come from? What are the statistical methods? An external validation is a study in itself and requires more explanation.
- How will missing data be handled? You have an extensive list of risk factors. It is likely that when combining data from multiple different studies, a very high proportion of these variables (if not 100%) will be incomplete. Therefore a robust missing data plan needs to be included.

- Minor point - I am not sure what is meant by "intoxications" (line 75)
- Please check the grammar of line 81. It does not read well. |

Reviewer: 1
Dr. LEDYCNARF DE HOLANDA, Universidade Federal do Rio Grande do Norte
Comments to the Author:
Dear authors,

Congratulations on the development of a new machine learning (ML) algorithm of great relevance for rotator cuff repair surgery and ML algorithm developers.

This manuscript outlines a protocol for a retrospective multicenter cohort study to develop and train an algorithm that can be used as an online available clinical prediction tool, to predict the risk of retear in patients undergoing rotator cuff repair. They propose to explore any datasets including at least 1000 patients.

This protocol can be useful for other similar research in the field of health professionals and algorithms developers. From this point of view, all this information should be clear in the whole manuscript, which I will describe below.

The methods section in the abstract needs to insert the name of each algorithm development step, and inform which metrics will be used to evaluate the algorithm.
Thank you, we have provided more extensive data on the steps and metrics for evaluating every algorithm to the protocol.
ML and artificial intelligence (AI) algorithms have been implemented to favor prediction and diagnosis of disease and support therapeutic decision making. From this perspective, how can this support your study? What gaps from previous studies will your research fill? I strongly suggest that all this information be in the introduction section.
A clear statement of the gap in current research this study aims to fill has been added

In the methods section, they should elaborately create a figure to summarize all the steps of algorithm development. Furthermore, I feel this section needs more information about what information about clinical examination findings should be considered as criteria? (1) what will be the algorithm labels? (2) what will be the features extractions? (3) how will they manage with missing data? (4) how will the statistical analysis be done? (5)
We have included all 5 points above in the rewritten methods section of our protocol. We have not included a figure but we did include an overview of the steps we are going to follow.
The discussion section of the paper lacks technicality and highlights its high contribution.
We have broadened the technical explanation of our approach in the methods section of the protocol. We agree there is little technical discussion, although we argue that this would be difficult if not impossible, as further analysis still has to point out which of the algorithms will be most successful. The technical discussion would be included in the publication of the final algorithm

Yours sincerely,
Reviewer
Dear dr Ledycnarf de Hollanda, thank you for your feedback. It has helped us to improve the explanation on the technical aspects of our manuscript.

Reviewer: 2
Dr. A van Noort, Spaarne Gasthuis

Comments to the Author:
Compliments to the authors for this very interesting and really important study. To my opinion there only are only a few, nevertheless important, questions to be answered.
In developing and training a machine learning algorithm it's offcourse essential to incorporate as much portentially influential factors as possible. Taking supplemental 2 into mind I miss patient related factors like:
1. Psychological factors eg: a medical history of depression, anxiety .
Symptoms of catastrophic behaviour. A medical history of difficult objectifiable disorders like fibromyalgia.
Even though we agree this could be a relevant patient related factor, this is not commonly reported in previous studies. Therefore it would have to be removed in analysis based on missing data.
2. Sports activity (level)
Sports activity level has been added as an input variable to the protocol and supplement 2
3. Work related factors: Workers compensation (yes/no) has been described as an important factor related to outcome after rotator cuff surgery.
Workers compensation has been added as an input variable to the protocol and supplement 2
I'm looking forard to receive the comments of the authors
Dear dr van Noort, thank you for your feedback. We will evaluate all patient related factors that will be provided to us by the data contributors. However, we need a significant number of cases to be presented with those variables in order to be able to use them, as explained in the newly added part on missing data.

Reviewer: 3
Dr. Rafael Pierami, instituto israelita de ensino e pesquisa do Hospital Albert Einstein, Grupo de Ombro e Cotovelo do Hospital Alvorara Moema
Comments to the Author:
Thank you for inviting me to review this protocol. The authors have made a significant effort, planning, developing and presenting their study protocol. I wish them well with the conduct of their study and look forward to the results.
Dear dr Rafael Pierami, thank you for your feedback. Thanks to you we were able to make many improvements to the writing and other details of our protocol.

1. Title: The authors report the protocol for a retrospective multicenter cohort study that aims to develop a clinical prediction tool to predict the retear risk in patients undergoing rotator cuff repair. However, since the primary outcomes defined were retear rate and enduring clinical outcomes, it seems to me that the study is covering more than just the retear rate probability. I would recommend that the functional outcome (enduring clinical outcomes) should be included in the title of the study.
The title has been changed into a more complete description of the study

2. Line 70 - On the first paragraph, the first reference (1) is dated from 2004; I would suggest that the authors replace it or add new data
Reference has been replaced with a more up to date study

3. Line 75- "Multiple leaders in shoulder surgery" seems to be a little ague in my opinion. I would recommend the authors to rephrase it.
The sentences has been rephrased without the use of the words between parentheses.

4. Line 77- It is established that worker's compensation claim is associated with poorer patient reported outcomes. I would suggest the authors to add this to the study protocol
Workers compensation has been added as an input variable to the protocol and supplement 2

5.   Line 79- the paragraph: "However, a majority… pathology-specific grading" denotes a less value feeling over these "daunted surgeons"; these surgeons are actually basing their practices on the available and recommended data. I would suggest the authors to rephrase the sentence
The part of the sentence that suggested negative feelings towards other surgeons has been removed

6.   Line 86- the references (9) and (11) are dated form 1992 and 2000; I would suggest the authors to add newer data
References have been updated

7.   Lines 91 to 94 – the study seems to encompass retear-chance and also the clinical improvement-chance. I would suggest that the authors add this information in this section
Secondary outcomes have been added to this part of the protocol

8.   Line 101- the authors did not define the time period in which they performed the systematic literature search. Since there was a significant evolution on the techniques and materials, it seems that this timeframe is important.
Search period has been included

9.   Line 108- the author performed the systematic search only on PubMed. Why not include other databases, such Scopus, EMBASE and Web of Science?
We have performed the initial search in the Pubmed database. Additional searches in other databases have not provided us with more studies so we have decided only to include the search in Pubmed. We are confident that Pubmed provides a complete overview of clinical studies.

10.   Line 109- The population of 1.000 patients seems to be large enough to address the question of the study. However, it is based on some statistical analysis? I would suggest the authors to be more specific on this issue
Thank you for this question. There is no standardized method to perform power analyses or calculate sample size for Machine Learning, therefore we have applied the 'rule of thumb' of at least 1000 patients with minimally 20% events. We have included this explanation in the manuscript.
11.   Line 113- The authors should explain how the randomization process will be or was performed
An explanation on how the randomization will be performed has been added

12.   Line 117- the Sugaya's classification for rotator cuff retear is not dichotomous. So, I would suggest the authors to be more specific on this subject
Explanation on the dichotomous representation of the Sugaya classification has been added

13.   Line 123- All the primary and secondary outcomes are categorical; so this information is not necessary
As all outcomes are categorical, this information has been removed

14.   Line 148- It seems to me that the algorithm, after all, will predict the patients with retear of rotator cuff AND unsatisfactory functional outcomes and not only patients with rotator cuff retear. I would suggest the author to be more clear and specific about this.
We have changed the sentence in order to specify that both groups will be evaluated

15.   Line 157- Ethics and Dissemination: the authors should explain whether they will make and how they will make the data obtained pblic
Information on data sharing has been moved to the paragraph on ethics and dissemination

16.   Line 171 and 172- The authors cite a recent meta-analysis however they did not mention or reference any. Please add the reference for this citation

Correct citation has been added

17.   Line 173 and 174- On the study conducted by Carbonel et. Al (21) the conclusion was that the clinical outcomes in patients with a partial thickness tear is similar to those with intact repair. The authors suggests that in patients with full thickness retear "there does appear to be a greater clinical and funciotnal impact". I would suggest the editor to advise the authors to rephrase this sentence. Correct citation has been added

18.   Line 185- I would suggest the authors to replace the word profit to benefit or similar Profit has been changed to benefit

19.   Lines 186 to 187- as previously said, the study seems to be covering more than the retear rate alone. I would suggest the authors to add the information that, after all, the algorithm will also predict the chance of a non enduring clinical outcome Retear has been changed to outcomes

20.   Line 189- in my opinion, the fact that this is a multicenter study is a strength of the study. If any variance on variables or missing data is noted, it should be elucidated on the results sections of the final paper The statement that variances in data between hospitals will be reported has been added to the protocol

Reviewer: 4
Dr. Richard Craig, University of Oxford
Comments to the Author:
Thank you for sharing this protocol. This seems to be a well thought out study concept. I would be grateful for some clarifications, particularly in the methods section.
Dear dr Richard Craig, thank you for all the provided feedback. It has helped us concretize several steps we will be taking course of the development.

- It took some time to understand that this study will be using individual participant data from existing studies. Please make this more explicit in the collecting data section.
More explicit mention of this has been added

- Whilst I recognise that this study is ongoing, please try to keep the tense of the writing consistent as it describes a piece of future work
Thank you, we have corrected the use of past tense.

- In the machine learning section - this needs expert statistical review.
Agreed. The execution of the machine learning will therefore take place in collaboration with the international machine learning professionals in our Consortium

- Is an 80:20 split the most efficient use of the data? Have bootstrapping methods been considered?
We agree that the internal validation part needed more thought. We have decided to go with cross validation using the established trainControl() function in R as an alternative to bootstrapping

- I am unfamiliar with the Felsch reference. Please expand the text here to speed out what complications you will be recording and how to grade them

We have extended our explanation on our approach to classifying adverse events. However, the feasibility of our approach depends mainly on the records of the original studies

- External validation - this needs to be properly described. Has an external validation study been planned? Where will the data come from? What are the statistical methods? An external validation is a study in itself and requires more explanation.

We completely agree that external validation is a study by itself. This is now more clearly described it the protocol

- How will missing data be handled? You have an extensive list of risk factors. It is likely that when combining data from multiple different studies, a very high proportion of these variables (if not 100%) will be incomplete. Therefore a robust missing data plan needs to be included.

A extended explanation on our missing data plan has been included

- Minor point - I am not sure what is meant by "intoxications" (line 75)
- Please check the grammar of line 81. It does not read well.

Both minor points have been rephrased.

VERSION 2 – REVIEW

REVIEWER	DE HOLANDA, LEDYCNARF Universidade Federal do Rio Grande do Norte, Fisioterapia
REVIEW RETURNED	03-Dec-2022

GENERAL COMMENTS	Thank you for giving me the opportunity to review the manuscript entitled " Developing a Machine Learning Algorithm to predict probability of retear and functional outcomes in patients undergoing rotator cuff repair surgery: A protocol for a retrospective multicenter study." for publication in BMJ Open. I hope that the authors will find my comment in satisfactory way, and I am willing to analyze the new corrections to this article. I am available to BMJ Open to review other manuscripts. This study is relevant to the clinical area, mainly to rotator cuff repair surgeon and engineering professionals who work on machine learning algorithm to prediction in health. I would like to recommend the authors checking the whole manuscript. I have identified minor typos that must be corrected. Yours sincerely, Ledycnarf Holanda

REVIEWER	van Noort, A Spaarne Gasthuis, Orthopedic surgery
REVIEW RETURNED	27-Nov-2022

GENERAL COMMENTS	I wish the authors well with the conduct of their study and look forward to the results. My remarks have sufficiently been answered and I agree with publication of the manuscript

REVIEWER	Pierami, Rafael instituto israelita de ensino e pesquisa do Hospital Albert Einstein, Sistema Locomotor

REVIEW RETURNED	14-Dec-2022

GENERAL COMMENTS	Thanks again for the opportunity to review this manuscript. All suggestions and doubts were corrected/clarified. I noticed a few minor misspellings over the text.
	1. Line 90 – there's a missing phrase "online available"
	2. Line 112- replace semicolon (;) after groups to colon(:)
	3. Line 136 – misspelled worldwide
	4. Line 151- remove the comma after compensation
	5. Line 188 – remove parentheses after trainControl

REVIEWER	Craig, Richard University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
REVIEW RETURNED	22-Nov-2022

GENERAL COMMENTS	Thank you for your hard work to improve the quality of the paper. It is much more robustly described now. My fellow reviewers had more initial queries than I did which seem to have been addressed, but the paper should also be viewed by one of them with statistical expertise.
	Best of luck with your project. A final note of caution… One reviewer quite rightly pointed out that psychosocial factors will be important. You do not feel that these can be included in your models due to an absence of data, which is true. But we know that these factors may well contribute far more than traditional surgical factors such as repair technique and tear size. I would therefore be prepared to be disappointed by how well your model performs, and to be cautious not to read too much into the results if it is overfitted. There is still much more to understand about this patient group.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4
Dr. Richard Craig, University of Oxford
Comments to the Author:
Thank you for your hard work to improve the quality of the paper. It is much more robustly described now. My fellow reviewers had more initial queries than I did which seem to have been addressed, but the paperhould also be viewed by one of them with statistical expertise.

Best of luck with your project. A final note of caution… One reviewer quite rightly pointed out that psychosocial factors will be important. You do not feel that these can be included in your models due to an absence of data, which is true. But we know that these factors may well contribute far more than traditional surgical factors such as repair technique and tear size. I would therefore be prepared to be disappointed by how well your model performs, and to be cautious not to read too much into the results if it is overfitted. There is still much more to understand about this patient group.

Dear Dr Craig, thank you for your helpful feedback. Fully noted on your comment of the need for expertise for statistics. I would like to address this concern. Being part of the Machine Learning Consortium, which is based around the international joint venture of Machine Learning specialists of the University of Groningen and Flinders University of Adelaide, all analyses will be repeatedly evaluated by experts in the field. This will results in much more in-depth and data-specific analyzation of the final data for the final paper.

Furthermore, we agree on the psychological factors as important confounder and will include this accordingly in the interpretation of our models.

Reviewer: 2
Dr. A van Noort, Spaarne Gasthuis
Comments to the Author:
I wish the authors well with the conduct of their study and look forward to the results.
My remarks have sufficiently been answered and I agree with publication of the manuscript.

Dear dr van Noort, thank you for your comments and feedback.

Reviewer: 1
Dr. LEDYCNARF DE HOLANDA, Universidade Federal do Rio Grande do Norte
Comments to the Author:
Thank you for giving me the opportunity to review the manuscript entitled " Developing a Machine Learning Algorithm to predict probability of retear and functional outcomes in patients undergoing rotator cuff repair surgery: A protocol for a retrospective multicenter study." for publication in BMJ Open.
I hope that the authors will find my comment in satisfactory way, and I am willing to analyze the new corrections to this article. I am available to BMJ Open to review other manuscripts.
This study is relevant to the clinical area, mainly to rotator cuff repair surgeon and engineering professionals who work on machine learning algorithm to prediction in health.

Dear dr Ledycnarf de Holanda,

Thank you for acknowledging the relevance of our research. We greatly value your feedfack on our protocol.

I would like to recommend the authors checking the whole manuscript. I have identified minor typos that must be corrected.

We have checked the whole document and corrected several minor typos.

Yours sincerely,
Ledycnarf Holanda

Reviewer: 3
Dr. Rafael Pierami, instituto israelita de ensino e pesquisa do Hospital Albert Einstein, Grupo de Ombro e Cotovelo do Hospital Alvorara Moema
Comments to the Author:
Thanks again for the opportunity to review this manuscript. All suggestions and doubts were corrected/clarified. I noticed a few minor misspellings over the text.

1. Line 90 – there's a missing phrase "online available"
2. Line 112- replace semicolon (;) after groups to colon(:)
3.
4. Line 151- remove the comma after compensation
5. Line 188 – remove parentheses after trainControl

Dear dr Pierami,

Thank you for your detailed description of typos. We have changed all 5 point you have mentioned. For point 5 we agree that even though the functions in R are commonly mentioned with their parentheses attached, for this text it is more suitable to leave them away.

*** ***

COI statements:

Reviewer: 4
Competing interests of Reviewer: No known conflicts.

Reviewer: 2
Competing interests of Reviewer: I have no compering interests.

Reviewer: 1
Competing interests of Reviewer: No competing interests.

Reviewer: 3
Competing interests of Reviewer: None.