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# BMJ Open

## Developing a Machine Learning Algorithm to predict retear probability in patients undergoing rotator cuff repair surgery: A protocol for a retrospective multicenter study.

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5 2 rotator cuff repair surgery: A protocol for a retrospective multicenter study.  
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3 39 **ABSTRACT**  
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6 40 **Purpose/Introduction:** The effectiveness of rotator cuff tear repair surgery is influenced by multiple  
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8 41 patient-related, pathology-centered and technical factors, which is thought to contribute to the reported  
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10 42 retear rates between 17 and 94%. Adequate patient selection is thought to be essential in reaching  
11  
12 43 satisfactory results. However, no clear consensus has been reached on which factors are most predictive  
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14 44 of successful surgery. A clinical decision tool that encompassed all aspects is still to be made. Artificial  
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16 45 Intelligence (AI) and machine learning algorithms use self-learning complex models that can be used to  
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18 46 make patient-specific decision-making tools.  
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22 47 The aim of this study is to develop and train an algorithm that can be used as an online available clinical  
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24 48 prediction tool, to predict the risk of retear in patients undergoing rotator cuff repair.  
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27 49 **Methods:** This is a retrospective multicenter cohort study. Patients undergoing rotator cuff repair and  
28  
29 50 evaluated by advanced imaging for healing at a minimum of 6 months after surgery were included. This  
30  
31 51 study consists of two parts. Part one: collecting all potential factors that might influence retear risks from  
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33 52 retrospective multicenter data, aiming to include >1000 patients worldwide. Part two: combining all  
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35 53 influencing factors into a model that can clinically be used as a prediction tool using machine learning.  
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39 54 **Ethics and dissemination:** For safe multicenter data exchange and analysis, our Machine Learning  
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41 55 Consortium adhered to the World Health Organization (WHO) regulation "Policy on Use and Sharing of  
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43 56 Data Collected by WHO in Member States Outside the Context of Public Health Emergencies." The study  
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45 57 results will be disseminated through publication in a peer-reviewed journal. IRB approval does not apply  
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47 58 to the current study protocol.  
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51 59 **Trial registration:** N/A  
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3 60 **ARTICLE SUMMARY**  
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- 6 61 - This study aims to calculate a patient-specific retear-chance after rotator cuff repair surgery.  
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8 62 - Creating an online-available tool that predicts retear chances can help both medical  
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10 63 professionals and patients in clinical decision-making on rotator cuff repair surgery.  
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12 64 - Included data will be gathered from previously published databases of all authors included in the  
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14 65 Machine Learning Consortium, aiming to include data from over 1000 patients.  
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17 66 - This study does have the limitation of being retrospective and therefore the study is dependent  
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19 67 on the recordkeeping of each individual hospital.  
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## 68 INTRODUCTION

69 Despite technical advances of rotator cuff repair, the rate of unhealed or re-torn rotator cuff tears  
70 remains high, with percentages ranging between 17 and 94% (1). A myriad of patient-related (2),  
71 pathology-centered (3) and technical factors (4) influence this adverse outcome.  
72 Patient selection is thought to be essential, however there is no consensus on which of the numerous  
73 potentially influential factors are most important for the prediction of satisfactory postoperative results  
74 (5). Furthermore, the value of preoperative optimization of potential comorbidities, metabolic  
75 deficiencies and intoxications remains questionable. Multiple leaders in shoulder surgery – convinced of  
76 patient-related influential factors – have implemented extensive preoperative screening and  
77 optimization programs prior to rotator cuff surgery. These include smoking cessation programs, diabetes  
78 control, use of statins in hyperlipidemia and vitamin D deficiency supplementing (2,6). However, a  
79 majority of shoulder surgeons – left daunted by the overwhelming and somewhat conflicting clinical  
80 evidence – seems to limit decision-making to more basic factors including age, functional demand and  
81 pathology-specific grading. Despite many different classification systems have been developed to  
82 facilitate decision making, a patient specific decision tool is still lacking (7,8).  
83 Artificial intelligence and machine learning (ML) is believed to facilitate a more patient-specific approach  
84 and will allow us to move to the next level of evidence-based medicine: personalized patient-care.  
85 Clinical prediction tools, incorporating patient specific factors to predict outcome probabilities will  
86 provide guidance to both clinicians and patients (9–11). Within orthopedic (oncology) surgery, prediction  
87 tools based on ML algorithms, have already been successfully implemented to predict patient specific 5-  
88 year survival in patients with chondrosarcoma (12). Furthermore, based on a series of 422 patients  
89 undergoing lumbar discectomy, Staartjes et al. demonstrated deep learning algorithms to be superior to  
90 standard regression models in predicting patient-reported outcome measures (PROMs) (11).

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3 91 The aim of this study is to develop and train a machine learning algorithm in order to create a clinical  
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5 92 prediction tool to be used in clinical practice by predicting retear-chance of the rotator cuff based on  
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7 93 preoperative patient data. The prediction tool will be free and online available.  
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## 11 12 13 95 **METHODS AND ANALYSIS**

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16 96 This study consists of two parts

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18 97 1. Collecting data
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20 98 2. Creating an online clinical prediction tool

### 21 22 23 24 99 **1. Collecting data**

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26 100 Step one involves collecting data from previously published studies in order to combine these into a  
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28 101 central database. Included were all randomized controlled trials comparing any surgical technique, add-  
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30 102 on biological intervention or rehabilitation protocols concerning rotator cuff surgery. In addition, cohorts  
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32 103 evaluating risk factors of surgical techniques after rotator cuff repair were included. This retrospective  
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34 104 review will therefore incorporate patients with all types of tears and concomitant procedures (e.g. biceps  
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36 105 tenodesis or tenotomy and acromioclavicular resection). Exclusion criteria for all studies was the lack of  
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38 106 postoperative evaluation by ultrasound, contrast-enhanced computed tomography or magnetic  
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40 107 resonance imaging at minimally 6 months after surgery. Relevant studies have been identified using a  
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42 108 systematic approach searching the online PubMed database according to the search terms found in  
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44 109 supplement 1. We aim to include at least 1000 patients in the database, all centers worldwide will be  
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49 110 able to contribute data.



## 111 **2. Machine Learning**

### 112 *Training Data & Test Data*

113 Eighty percent (80%) of all (>1000) patients included in the Machine Learning Consortium Database will  
114 be randomly allocated to the training dataset and 20% to the test dataset.

### 115 *Outcome variables*

#### 116 Primary outcome measures (dichotomous)

- 117 - Rotator cuff retear rates at minimum 6 months follow-up (yes vs no, specified by Sugaya  
118 Classification (13)) as measured on magnetic resonance imaging, arthro-CT and/or ultrasound.
- 119 - Enduring satisfactory functional outcome defined as achievement (yes vs no) and maintenance  
120 (yes vs no) of the PROM-specific MCID (14) in numeric rating scales of PROMs from baseline at 2-  
121 5 years follow-up after repair (PROMs include the Constant-Murley score, ASES, UCLA, OSS,  
122 WORC, DASH).

#### 123 Secondary outcome measures (categorical)

- 124 - Adverse events graded as the possibility of none/minor vs moderate/severe complication as  
125 defined in accordance to Felsch et al. and specified as infection, revision surgery or other (15).

### 126 *Input Variables*

127 For each respective primary outcome, a Random-Forest will be created based on all available data points  
128 in the Machine Learning Consortium Database to identify the variables with the highest predictive  
129 values. The data points available include patient demographic (sex, age), patient specific factors (BMI,  
130 dominance), pathology specific factors (e.g. tear size and location), surgical technique and add-on  
131 interventions. For a complete overview of all variables see supplement 2.

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3 132 Machine learning algorithm: development and testing  
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6 133 *Algorithms to be trained*  
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9 134 Based on previous studies (16,17), the following algorithms are likely to result in accurate prediction  
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11 135 models for our primary outcomes: 1) Bayes Point Machine 2) Boosted Decision Tree 3) Penalized  
12  
13 136 Logistical Regression 4) Neural Network 5) Support Vector Machine. In order to recognize patterns  
14  
15 137 related to each outcome, the machine learning algorithms will have to be trained separately for each  
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17 138 outcome.  
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21 139 *Assessing the performance of the algorithms on the test set*  
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24 140 The test-set consisting of 20% of the remaining data will be used to assess the performance of these  
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26 141 respective machine learning algorithms. The performance of the ML-algorithms will be assessed and  
27  
28 142 compared based on 1) model discrimination 2) calibration and 3) overall model performance (Brier  
29  
30 143 Score) according to Steyerberg's structured 'ABCD-methodology' for clinical prediction rules (18,19).  
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33 144 Accuracy, sensitivity, specificity and area under the ROC-curve are measures for a model's ability to  
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35 145 distinguish patients with the primary outcome from those without.  
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38 146 *Development decision rule*  
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41 147 The best performing algorithm will be deployed as an open-access probability calculator and used to  
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43 148 design a clinical decision rule. To simulate the clinical scenario to which a decision rule would be most  
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45 149 applicable, thresholds shall be selected based on patients with clinical symptoms of a re-tear with an  
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47 150 unsatisfactory functional outcome. The technical appendix and statistical code will be published.  
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3 151 *Blinding of data and external validation*  
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6 152 The researchers that will perform the statistical analysis and development of machine learning

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8 153 algorithms will be blinded of the origin of the data. Before incorporating the best performing algorithm

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10 154 will be externally validated. The same performance metrics will be calculated as described above.  
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13 155 *Patients and public involvement*  
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16 156 Patients and the public were not involved in the making of this protocol.  
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19 157 **ETHICS AND DISSEMINATION**  
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22 158 For safe multicentre data exchange and analysis, our Machine Learning Consortium adhered to the

23  
24 159 World Health Organization (WHO) regulation 'Policy on Use and Sharing of Data Collected by WHO in

25  
26 160 Member States Outside the Context of Public Health Emergencies' (20). As IRB has been acquired for

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28 161 each of the included studies and data are anonymized as in conventional meta-analyses, an additional

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30 162 IRB request does not apply to the current study protocol.  
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34 163 **CURRENT STATUS**  
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36 164 The study has currently entered the data-collection phase, which is expected to last until mid-2022. Re-

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38 165 evaluation of the data using machine learning algorithms to predict outcomes will start in September

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40 166 2022, after which the algorithms can be externally validated. The expected time of completion is by the

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43 167 mid-2023.  
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## 168 **DISCUSSION**

169 Due to the wide variety of pathological factors at the origin of rotator cuff tears and the numerous  
170 surgical approaches to repair, optimal decision-making remains challenging. Smaller case series often  
171 provide heterogeneous data on this topic, however the largest and most recent meta-analysis to date  
172 including 2,611 patients with a mean follow-up of 25 months has somewhat demystified the matter.  
173 Patients with a full-thickness rotator cuff retear exhibited significantly lower functional outcome scores  
174 and strength compared with patients with an intact or partially torn rotator cuff (21). This is  
175 corroborated by the findings of rotator cuff repair with more than 10 years follow-up, showing clinical  
176 superiority of structural tendon integrity in partial cuff tears (22,23). Progressive osteoarthritic changes  
177 are significantly more common in patients with repair failures (23). The most recent RCT comparing  
178 surgical repair to conservative treatment for degenerative rotator cuff tears showed that only operated  
179 patients without retear had an improvement exceeding the minimal clinical important difference (MCID)  
180 in functional outcome at 1 year follow-up (24). Findings from the latest meta-analysis on this  
181 comparative topic conclude that as the success rate of conservative treatment may be high, judicious  
182 selection of patients who are most likely to benefit from surgery is key (25). It is extremely difficult to  
183 combine all these factors into a clinical decision related to one specific patient. Creating a free online  
184 available clinical prediction tool that takes all these factors into account will assist physicians in selecting  
185 which patients with rotator cuff tears will profit from a repair. In addition, the aimed size (more than  
186 1000 patients) of the database that will be used to design and train the prediction tool might provide  
187 new insights on which biological or biomechanical factors influence retear risk the most. Awareness of  
188 these factors would be the essential first step to incorporating them in future treatment strategies and  
189 eventually improving outcomes. The main limitation of this study is that it is a retrospective, multicenter  
190 study. This means this study is dependent on the quality of recordkeeping in the different participating  
191 hospitals. This may lead to variance in recorded variables and therefore missing data.

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3 **192 AUTHOR STATEMENT**  
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6 **193** Laurens J.H. Allaart, Sanne H. van Spanning, Geert Alexander Buijze and Michel P.J van den Bekerom  
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8 **194** contributed to the conception, overall design and planning of the study. Laurent A.M. Hendrickx and Job  
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10 **195** N. Doornberg contributed to the conception and design of the methods section, primarily focussing on  
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12 **196** the machine learning section and data analysis. Alexander Lädemann, George S. Athwall, Thibault  
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15 **197** Lafosse and Laurent Lafosse contributed to the design of the methods section and primarily focussed on  
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17 **198** how the data should be collected and interpreted. Laurens J.H. Allaart, Sanne H. van Spanning, Geert  
18  
19 **199** Alexander Buijze and Michel P.J. van den Bekerom contributed to writing the protocol. All authors  
20  
21 **200** revised this version of the protocol and gave final approval for it to be published. All authors ensure that  
22  
23 **201** questions related to the accuracy or integrity of any part of this protocol are appropriately investigated  
24  
25  
26 **202** and resolved.  
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29 **203 CONTRIBUTOR STATEMENT**  
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32 **204** Vivek Pandey, Mats Ranebo, Martyn Snow and Riccardo d'Ambrosi have contributed by providing  
33  
34 **205** relevant feedback on the general design of the study.  
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3 206 **CONFLICTS OF INTEREST**  
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6 207 Dr Alexandre Lädermann is a paid consultant for Arthrex, Medacta and Stryker. He receives  
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30 217 after Rotator Cuff Repair'.  
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1  
2  
3 #1 subject

4 Rotator cuff tear/ injury

5  
6 **(rotator[tiab] AND cuff[tiab] AND injur\*[tiab])**

7 **OR**

8  
9 **(rotator[tiab] AND cuff[tiab] AND tear\*[tiab])**

10 **OR**

11  
12 **(rotator[tiab] AND cuff[tiab] AND repair\*[tiab])**

13 **OR**

14  
15 **(rotator[tiab] AND cuff[tiab] AND surg\*[tiab])**

16 **OR**

17 **"Rotator Cuff Injuries"[Mesh]**

18  
19 #2.1 Intervention (RCT)

20 Repair

21  
22 #2.2 Intervention (Cohort)

23 Repair

24  
25 #3 Outcome

26 Retear rate measured by MRI ultrasound or arthro CT

27  
28 **(Retear[tiab] OR (re-tear)[tiab] OR healing[tiab])**

29 **OR**

30 **("Magnetic Resonance Imaging"[Mesh] OR "MRI" OR "magnetic resonance"**

31 **OR**

32 **ultraso\*[tiab] OR "Ultrasonography"[Mesh]**

33 **OR**

34 **"Arthrography"[Mesh] OR arthrography[tiab])**

35  
36  
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44  
45  
46 Search: **((Retear[tiab] OR re-tear[tiab] OR healing[tiab]) OR ("Magnetic Resonance**  
47 **Imaging"[Mesh] OR "MRI" OR "magnetic resonance" OR ultraso\*[tiab] OR**  
48 **"Ultrasonography"[Mesh] OR "Arthrography"[Mesh] OR arthrography[tiab]) ) AND**  
49 **((rotator[tiab] AND cuff[tiab] AND injur\*[tiab]) OR (rotator[tiab] AND cuff[tiab] AND**  
50 **tear\*[tiab]) OR (rotator[tiab] AND cuff[tiab] AND repair\*[tiab]) OR (rotator[tiab] AND**  
51 **cuff[tiab] AND surg\*[tiab]) OR "Rotator Cuff Injuries"[Mesh]) Filters: Clinical Trial,**  
52 **Randomized Controlled Trial Sort by: Most Recent**  
53  
54  
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We will collect the following potential risk factors from the electronic medical records. The variables are mostly binary to make them compatible for all machine learning algorithms. Cut-off values will be used for the non-binary values. In case of doubt, overlap or less specific grouping than in this database, variables will be rounded up.

#### Patient characteristics

- Identification number
- Date of birth
- Sex
- Dominant side (yes/no)
- Chronicity of tear (<6 weeks / >6weeks)
  - Time from trauma to 1<sup>st</sup> treatment day
- ASA classification (1-4)

#### Biological factors

- Obesity (BMI <30 / ≥30)
- Cardiovascular disease incl. hypertension (yes / no)
- Smoking history (current smoker / non-smoker)
- Diabetes (yes/no; insulin dependent yes/no)
- Osteoporosis (yes/no)
- Hyperlipidemia (yes/no)
- Hypercholesterolemia (yes/no)
- Vitamin D deficiency (yes/no)
- NSAID use (yes/no)
- Thyroid dysfunction (no disease / hypothyroid / hyperthyroid)

#### Pathology characteristics (graded by by MRI or arthro CT)

- Tear location (posterolateral / anterosuperior)
- Size of tear (small (<1 cm), medium (1–3 cm), large (3–5 cm), or massive (>5 cm))
  - Size in the saggital oblique plane
- Fatty infiltration (Goutallier 0 - 4)
- Muscle atrophy as graded by tangent sign (yes / no)
- Tendon retraction (Patte 1 - 3)

#### Surgical Technique

- Single row (yes / no)
- Double row (yes / no)
- Suture bridge (yes no)
- Performing surgeon (surgeon / resident / fellow)

#### Rehabilitation protocol

- Timing of active mobilization (<6wks ≥ 6wks)

#### Add-on Intervention

- Biceps tenotomy/tenodesis (yes / no)
- Bone marrow stimulation by microfracturing footprint (yes/no)

- 1
- 2
- 3 ○ Steroid injections within year prior to surgery (0 / 1 / ≥2 injections)
- 4 ○ Augmentation with subacromial inflatable device (yes/no)
- 5 ○ Augmentation/bridging with patches/scaffolds/extracellular matrices (yes/no)
- 6 ○ Local injectable biologics (yes/no) including:
- 7     ▪ Platelet-rich plasma (P-PRP, L-PRP)
- 8     ▪ Leukocyte and platelet-rich fibrin (L-PRF)
- 9     ▪ Growth factors
- 10    ▪ Cell therapy (bone marrow stem cells / BMAC MSCs)
- 11 ○ Systemic drugs - Statins (yes/no)
- 12 ○ Systemic drugs - Vitamin D supplementation (yes/no)
- 13 ○ Systemic drugs - Vitamin C supplementation (yes/no)
- 14 ○ Systemic drugs – NSAIDs from >6 weeks postop (yes/no)
- 15
- 16
- 17

### 18 Outcomes

- 19 ○ Retear at minimum 6 months (yes no)
- 20 ○ Type of retear (Sugaya 1-5)
- 21 ○ Adverse event
- 22     ▪ None/mild (none reported) / Moderate/severe (reported adverse event)
- 23     ▪ Type of adverse event (Infection/revision/stiffness/other)
- 24 ○ PROMS
- 25     ▪ Type of PROM
- 26     ▪ Time of measurement (in days from surgery)
- 27     ▪ Consistency of PROM (yes/no)
- 28         • *Will be seperately formulated per PROM based on MCID*
- 29         • *improvement/consistency*
- 30         • *As the calculation of this variable will be greatly dependent on which*
- 31         • *PROMS and follow-up duration will be submitted by co-authors, we prefer*
- 32         • *to receive 'raw' data.*
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# BMJ Open

## 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.

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3 1 **TITLE:** Developing a Machine Learning Algorithm to predict probability of retear and functional outcomes  
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5 2 in patients undergoing rotator cuff repair surgery: A protocol for a retrospective multicenter study.  
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26 10 Bekerom<sup>2,3</sup>, and Geert Alexander<sup>1,6,10</sup> Buijze on behalf of the Machine Learning Consortium  
27  
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18 29  
19

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21  
22 31 Intelligence  
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3 35 **ABSTRACT**  
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6 36 **Purpose/Introduction:** The effectiveness of rotator cuff tear repair surgery is influenced by multiple  
7  
8 37 patient-related, pathology-centered and technical factors, which is thought to contribute to the reported  
9  
10 38 retear rates between 17 and 94%. Adequate patient selection is thought to be essential in reaching  
11  
12 39 satisfactory results. However, no clear consensus has been reached on which factors are most predictive  
13  
14  
15 40 of successful surgery. A clinical decision tool that encompassed all aspects is still to be made. Artificial  
16  
17 41 Intelligence (AI) and machine learning algorithms use self-learning complex models that can be used to  
18  
19 42 make patient-specific decision-making tools.  
20  
21

22 43 The aim of this study is to develop and train an algorithm that can be used as an online available clinical  
23  
24 44 prediction tool, to predict the risk of retear in patients undergoing rotator cuff repair.  
25  
26

27 45 **Methods:** This is a retrospective multicenter cohort study. Patients undergoing rotator cuff repair and  
28  
29 46 evaluated by advanced imaging for healing at a minimum of 6 months after surgery were included. This  
30  
31 47 study consists of two parts. Part one: collecting all potential factors that might influence retear risks from  
32  
33 48 retrospective multicenter data, aiming to include >1000 patients worldwide. Part two: combining all  
34  
35 49 influencing factors into a model that can clinically be used as a prediction tool using machine learning.  
36  
37  
38

39 50 **Ethics and dissemination:** For safe multicenter data exchange and analysis, our Machine Learning  
40  
41 51 Consortium adhered to the World Health Organization (WHO) regulation "Policy on Use and Sharing of  
42  
43 52 Data Collected by WHO in Member States Outside the Context of Public Health Emergencies." The study  
44  
45 53 results will be disseminated through publication in a peer-reviewed journal. IRB approval does not apply  
46  
47 54 to the current study protocol.  
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51 55 **Trial registration:** N/A  
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3 56 **ARTICLE SUMMARY**  
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6 57 **Strengths and Limitations of this study**  
7

- 8 58 - This study aims to calculate a patient-specific retear-chance after rotator cuff repair surgery  
9  
10 59 - Creating an online-available tool that predicts retear chances can help both medical  
11  
12 professionals and patients in clinical decision-making on rotator cuff repair surgery  
13 60  
14  
15 61 - Included data will be gathered from previously published databases of all authors included in the  
16  
17 62 Machine Learning Consortium, aiming to include data from over 1000 patients.  
18  
19 63 - This study does have the limitation of being retrospective and therefore the study is dependent  
20  
21 64 on the recordkeeping of each individual hospital.  
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## 65 INTRODUCTION

66 Despite technical advances of rotator cuff repair, the rate of unhealed or re-torn rotator cuff tears  
67 remains high, with percentages ranging between 10 and 94% (1). A myriad of patient-related (2),  
68 pathology-centered(3) and technical factors(4) influence this adverse outcome.  
69 Patient selection is thought to be essential, however there is no consensus on which of the numerous  
70 potentially influential factors are most important for the prediction of satisfactory postoperative results  
71 (5). Furthermore, the value of preoperative optimization of potential patient-related influential factors  
72 including comorbidities, metabolic deficiencies and intoxications remains questionable. The increasing  
73 worldwide interest in these factors is confirmed by development of preoperative screening and  
74 optimization programs aiming for smoking cessation, diabetes control, use of statins in hyperlipidemia  
75 and vitamin D deficiency supplementing (2,6). However, the majority of shoulder surgeons seems to limit  
76 decision-making to more basic, previously established predictive factors including age, functional  
77 demand and pathology-specific grading. Despite the many different classification systems that have been  
78 developed to facilitate decision making, a patient specific decision tool is still lacking (7,8). This, in  
79 combination with the fact that existing research commonly evaluates a single treatment option between  
80 homogenic groups, makes it almost impossible for surgeons to preoperatively indicate a reliable chance  
81 of satisfactory results.  
82 Artificial intelligence and machine learning (ML) is believed to facilitate a more patient-specific approach  
83 and will allow us to move to the next level of evidence-based medicine: personalized patient-care.  
84 Clinical prediction tools, incorporating patient specific factors to predict outcome probabilities will  
85 provide guidance to both clinicians and patients (9,10). Within orthopedic (oncology) surgery, prediction  
86 tools based on ML algorithms, have already been successfully implemented to predict patient specific 5-  
87 year survival in patients with chondrosarcoma (11). Furthermore, based on a series of 422 patients

1  
2  
3 88 undergoing lumbar discectomy, Staartjes et al. demonstrated deep learning algorithms to be superior to  
4  
5 89 standard regression models in predicting patient-reported outcome measures (PROMs)(9).  
6  
7

8 90 online available.  
9

### 10 91 **Aim of this study**

11  
12  
13 92 The aim of this study is to develop and train a machine learning algorithm in order to create a clinical  
14  
15 93 prediction tool to be used in clinical practice by predicting retear-chance of the rotator cuff as well as  
16  
17 94 chance of clinical improvement based on preoperative patient data. The prediction tool will be free and  
18  
19  
20 95 online available  
21  
22

### 23 96 **METHODS AND ANALYSIS**

24  
25  
26 97 The primary and secondary outcome measures will be implemented as features for the prediction  
27  
28 98 algorithm.  
29  
30

#### 31 99 Primary outcome measures

- 32  
33  
34 100 - Rotator cuff retear rates at minimum 6 months follow-up as measured on magnetic resonance  
35  
36 101 imaging, arthro-CT and/or ultrasound (yes vs no, defined by Sugaya grade 1-3 as no retear and  
37  
38 102 grade 4-5 as retear (12)).  
39  
40  
41 103 - Enduring satisfactory functional outcome defined as achievement (yes vs no) and maintenance  
42  
43 104 (yes vs no) of the PROM-specific MCID(13) in numeric rating scales of PROMs from baseline at 2-  
44  
45 105 5 years follow-up after repair (PROMs include the Constant-Murley score, ASES, UCLA, OSS,  
46  
47 106 WORC, DASH).  
48  
49

#### 50 107 Secondary outcome measures

- 51  
52  
53 108 - Adverse events graded as the possibility of none/minor vs moderate/severe complication as  
54  
55 109 defined in accordance to Felsch et al. (14). Adverse events classify as moderate/severe from  
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3 110 Felsch class III onwards, which means when other surgical or radiologic intervention was needed  
4  
5 111 or unexpected hospital admission was necessary. Adverse events will be differentiated into three  
6  
7 112 groups; infection, revision surgery or other.  
8  
9

### 10 113 **Model development**

11  
12  
13 114 The development of the prediction model will be performed based on the steps described by Steyerberg  
14  
15 115 et al (15):

- 16 116 1. Data collection
- 17  
18 117 2. Data inspection
- 19  
20 118 3. Coding of predictors
- 21  
22 119 4. Model specification
- 23  
24 120 5. Model estimation and performance
- 25  
26 121 6. Model validation
- 27  
28 122 7. Model presentation
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#### 34 123 **1. Data collection**

35  
36  
37 124 Step one will involve contacting authors from previously published studies in order to collect and  
38  
39 125 combine their (raw) individual patient data into a central database. All randomized controlled trials  
40  
41 126 comparing any surgical technique, add-on biological intervention or rehabilitation protocols concerning  
42  
43 127 rotator cuff surgery will be included. In addition, cohorts evaluating risk factors of surgical techniques  
44  
45 128 after rotator cuff repair will be included. This retrospective review will therefore incorporate patients  
46  
47 129 with all types of tears and concomitant procedures (e.g. biceps tenodesis or tenotomy and  
48  
49 130 acromioclavicular resection). Exclusion criteria for all studies will be the lack of postoperative evaluation  
50  
51 131 by ultrasound, contrast-enhanced computed tomography or magnetic resonance imaging at minimally 6  
52  
53 132 months after surgery, or publication date from before 2005. Relevant studies will be identified using a  
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3 133 systematic approach primarily searching the online PubMed database according to the search terms  
4  
5 134 found in supplement 1. As there is no golden standard for sample size or power calculations for  
6  
7 135 prediction models, and we are fully dependent on contributed data, we aim to include at least 1000  
8  
9 136 patients world wide (15).

## 137 **2. Problem definition and data inspection**

138 All contributed data sets will be formatted into one central database. As data is commonly collected in  
139 .csv (Microsoft Excel) or .sav (SPSS) files, formatting will be performed with the dplyr package for R  
140 software. All raw data of the different variables will be separately reviewed for inaccuracies and other  
141 defects. This process will focus on uniformization of possible inconsistencies in the collected data, for  
142 example follow-up times into a standardized format as 'days after surgery'. Categorical data will be  
143 translated into English or corrected for typographs. Continuous variables will be screened for outliers by  
144 visualization in the ggplot package. Impossible values or uninterpretable syntax errors will be excluded  
145 from the central database.

## 147 **3. Coding of predictors**

148 For each primary outcome, a logistic regression will be performed including all available variables in the  
149 central database to identify the variables with the highest predictive values. The data points available  
150 include patient demographic (sex, age), patient specific factors (BMI, dominance, sport/activity level,  
151 workers compensation,), pathology specific factors (e.g. tear size and location), surgical technique and  
152 add-on interventions. For a complete overview of all variables see supplement 2. The variables with the  
153 highest predictive values will be used as the algorithms labels.

154

1  
2  
3 155 *Missing data*  
4  
5

6 156 As the main database will comprise data from multiple studies, we expect many cases of missing data.  
7

8 157 The approach to missing data will differ depending on the type of variable. Variables with less than 5%  
9

10 158 missing data will be replaced by imputation (16). Missing data on any surgical technique or add-on  
11

12 159 intervention is expectable as interventions outside the scope of a study would not be mentioned (or  
13

14 160 briefly mentioned in the exclusions part). Therefore this kind of missing data will be transformed to 'No'.  
15

16 161 Overall availability of variables will be presented according to current guidelines (17). Any variances  
17

18 162 between hospitals will be reported.  
19  
20  
21

22 163 **4. Model specification**  
23  
24

25 164 *Algorithms to be trained*  
26  
27

28 165 Based on previous studies (18,19), the following algorithms are likely to result in accurate prediction  
29

30 166 models for our primary outcomes: 1) Bayes Point Machine 2) Boosted Decision Tree 3) Penalized  
31

32 167 Logistical Regression 4) Neural Network 5) Support Vector Machine. In order to recognize patterns  
33

34 168 related to each outcome, the machine learning algorithms will have to be trained separately for each  
35

36 169 outcome.  
37  
38  
39

40 170 **5. Model estimation and performance**  
41  
42

43 171 *Assessing the performance of the algorithms*  
44  
45

46 172 The performance of the ML-algorithms will be assessed and compared based on 1) model discrimination;  
47

48 173 2) calibration and 3) overall model performance (Brier Score) according to Steyerberg's structured  
49

50 174 'ABCD-methodology' for clinical prediction rules (15,20).  
51  
52

53 175 The model's predicted probability is plotted against the actual observed probability to calculate  
54

55 176 calibration of a model. Perfect models will have calibration intercepts of 0, and calibration slopes of 1.27  
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3 177 The overall performance of the model will be assessed with the Brier-score. A perfect Brier score,  
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5 178 indicating total accuracy, is a score of 0. The lowest possible score is a Brier score of 1.26. Accuracy,  
6  
7 179 sensitivity, specificity and area under the ROC-curve are measures for a model's ability to distinguish  
8  
9  
10 180 patients with the primary outcome from those without.

## 11 12 181 **6. Model validation**

### 13 14 15 182 *Internal validation*

16  
17  
18 183 Internal validation of our algorithms will be performed by 10-fold cross validation. This means that  
19  
20 184 instead of dividing the main data set into one training set and one testing set, this process will be 10  
21  
22 185 times randomly repeated and the results will be averaged. This has as main advantage that all individual  
23  
24 186 patient records are used as training and testing data simultaneously, which results in higher accuracy of  
25  
26  
27 187 predictions as well as lower chance of bias. The cross validation will be performed using the  
28  
29 188 trainControl() function from the Caret library for R.

### 30 31 32 189 *External validation*

33  
34  
35 190 Before incorporating the best performing algorithm, we aim to have the algorithm externally validated.  
36  
37 191 The same performance metrics could be calculated as described above. However, this would involve  
38  
39 192 collaboration with partners that have adequate data and are willing to share. As no agreements currently  
40  
41 193 have been made, the external validation is outside the scope of this study.

## 42 43 44 194 **7. Model presentation**

45  
46  
47 195 The best performing algorithm will be deployed as an open-access probability calculator and used to  
48  
49 196 design a clinical decision rule. To simulate the clinical scenario to which a decision rule would be most  
50  
51 197 applicable, thresholds shall be selected based on patients with clinical symptoms of a re-tear or with an  
52  
53  
54 198 unsatisfactory functional outcome.

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3 199 **ETHICS AND DISSEMINATION**

4  
5 200 For safe multicentre data exchange and analysis, our Machine Learning Consortium adhered to the  
6  
7 201 World Health Organization (WHO) regulation 'Policy on Use and Sharing of Data Collected by WHO in  
8  
9 202 Member States Outside the Context of Public Health Emergencies.'<sup>(21)</sup> As IRB has been acquired for  
10  
11 203 each of the included studies and data are anonymized as in conventional meta-analyses, an additional  
12  
13  
14 204 IRB request does not apply to the current study protocol. The technical appendix, statistical code and  
15  
16 205 final dataset will be published with the original article.  
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19 206 **PATIENT AND PUBLIC INVOLVEMENT**

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21  
22 207 Patients and the public were not involved in the making of this protocol.  
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24

25 208 **CURRENT STATUS**

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27 209 The study has currently entered the data-collection phase, which is expected to last until end-2022. Re-  
28  
29 210 evaluation of the data using machine learning algorithms to predict outcomes will start in December  
30  
31 211 2022, after which the algorithms can be externally validated. The expected time of completion is by the  
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34 212 mid-2023.  
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3 213 **DISCUSSION**  
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5 214 Due to the wide variety of pathological factors at the origin of rotator cuff tears and the numerous  
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7 215 surgical approaches to repair, optimal decision-making remains challenging. Smaller case series often  
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9 216 provide heterogeneous data on this topic, however the largest and most recent meta-analysis to date  
10  
11 217 including 2,611 patients with a mean follow-up of 25 months has somewhat demystified the matter.  
12  
13 218 Patients with a full-thickness rotator cuff retear exhibited significantly lower functional outcome scores  
14  
15 219 and strength compared with patients with an intact or partially torn rotator cuff (22). This is  
16  
17 220 corroborated by the findings of rotator cuff repair with more than 10 years follow-up, showing clinical  
18  
19 221 superiority of structural tendon integrity in partial cuff tears(23–25). Progressive osteoarthritic changes  
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21 222 are significantly more common in patients with repair failures.(24) The most recent RCT comparing  
22  
23 223 surgical repair to conservative treatment for degenerative rotator cuff tears showed that only operated  
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25 224 patients without retear had an improvement exceeding the minimal clinical important difference (MCID)  
26  
27 225 in functional outcome at 1 year follow-up (26). Findings from the latest meta-analysis on this  
28  
29 226 comparative topic conclude that as the success rate of conservative treatment may be high, judicious  
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31 227 selection of patients who are most likely to benefit from surgery is key (27). It is extremely difficult to  
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33 228 combine all these factors into a clinical decision related to one specific patient. Creating a free online  
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35 229 available clinical prediction tool that takes all these factors into account will assist physicians in selecting  
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37 230 which patients with rotator cuff tears will benefit from a repair. In addition, the aimed size (more than  
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39 231 1000 patients) of the database that will be used to design and train the prediction tool might provide  
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41 232 new insights on which biological or biomechanical factors influence outcomes after rotator cuff repair  
42  
43 233 the most. Awareness of these factors would be the essential first step to incorporating them in future  
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45 234 treatment strategies and eventually improving outcomes. The main limitation of this study is that it is a  
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47 235 retrospective, multicenter study. This means this study is dependent on the quality of recordkeeping in  
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3 236 the different participating hospitals. This may lead to variance in recorded variables and therefore  
4  
5 237 missing data.

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8 238 **AUTHOR CONTRIBUTIONS**  
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10  
11 239 Laurens J.H. Allaart, Sanne H. van Spanning, Geert Alexander Buijze and Michel P.J van den Bekerom  
12  
13 240 contributed to the conception, overall design and planning of the study. Laurent A.M. Hendrickx and Job  
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15 241 N. Doornberg contributed to the conception and design of the methods section, primarily focussing on  
16  
17 242 the machine learning section and data analysis. Alexander Lädermann, George S Athwal, Thibault Lafosse  
18  
19 243 and Laurent Lafosse contributed to the design of the methods section and primarily focussed on how the  
20  
21 244 data should be collected and interpreted. Laurens J.H. Allaart, Sanne H. van Spanning, Geert Alexander  
22  
23 245 Buijze and Michel P.J. van den Bekerom contributed to writing the protocol. All authors revised this  
24  
25 246 version of the protocol and gave final approval for it to be published. All authors ensure that questions  
26  
27 247 related to the accuracy or integrity of any part of this protocol are appropriately investigated and  
28  
29 248 resolved.  
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3 252 **CONFLICTS OF INTEREST**  
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5

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26  
27  
28 262 The Effect of Risk Factors, Surgical Technique and Biomodulation on Tendon Healing  
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31 263 after Rotator Cuff Repair'.  
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- 51 335

1  
2  
3 #1 subject

4 Rotator cuff tear/ injury

5  
6 **(rotator[tiab] AND cuff[tiab] AND injur\*[tiab])**

7 **OR**

8  
9 **(rotator[tiab] AND cuff[tiab] AND tear\*[tiab])**

10 **OR**

11  
12 **(rotator[tiab] AND cuff[tiab] AND repair\*[tiab])**

13 **OR**

14  
15 **(rotator[tiab] AND cuff[tiab] AND surg\*[tiab])**

16 **OR**

17 **"Rotator Cuff Injuries"[Mesh]**

18  
19 #2.1 Intervention (RCT)

20 Repair

21  
22 #2.2 Intervention (Cohort)

23 Repair

24  
25 #3 Outcome

26 Retear rate measured by MRI ultrasound or arthro CT

27  
28 **(Retear[tiab] OR (re-tear)[tiab] OR healing[tiab])**

29 **OR**

30 **("Magnetic Resonance Imaging"[Mesh] OR "MRI" OR "magnetic resonance"**

31 **OR**

32 **ultraso\*[tiab] OR "Ultrasonography"[Mesh]**

33 **OR**

34 **"Arthrography"[Mesh] OR arthrography[tiab])**

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46 Search: **((Retear[tiab] OR re-tear[tiab] OR healing[tiab]) OR ("Magnetic Resonance**  
47 **Imaging"[Mesh] OR "MRI" OR "magnetic resonance" OR ultraso\*[tiab] OR**  
48 **"Ultrasonography"[Mesh] OR "Arthrography"[Mesh] OR arthrography[tiab]) ) AND**  
49 **((rotator[tiab] AND cuff[tiab] AND injur\*[tiab]) OR (rotator[tiab] AND cuff[tiab] AND**  
50 **tear\*[tiab]) OR (rotator[tiab] AND cuff[tiab] AND repair\*[tiab]) OR (rotator[tiab] AND**  
51 **cuff[tiab] AND surg\*[tiab]) OR "Rotator Cuff Injuries"[Mesh]) Filters: Clinical Trial,**  
52 **Randomized Controlled Trial Sort by: Most Recent**  
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We will collect the following potential risk factors from the electronic medical records. The variables are mostly binary to make them compatible for all machine learning algorithms. Cut-off values will be used for the non-binary values. In case of doubt, overlap or less specific grouping than in this database, variables will be rounded up.

#### Patient characteristics

- Identification number
- Date of birth
- Sex
- Dominant side (yes/no)
- Chronicity of tear (<6 weeks / >6weeks)
  - Time from trauma to 1<sup>st</sup> treatment day
- ASA classification (1-4)
- Sport/activity level
- Receiving workers compensation (yes/no)

#### Biological factors

- Obesity (BMI <30 / ≥30)
- Cardiovascular disease incl. hypertension (yes / no)
- Smoking history (current smoker / non-smoker)
- Diabetes (yes/no; insulin dependent yes/no)
- Osteoporosis (yes/no)
- Hyperlipidemia (yes/no)
- Hypercholesterolemia (yes/no)
- Vitamin D deficiency (yes/no)
- NSAID use (yes/no)
- Thyroid dysfunction (no disease / hypothyroid / hyperthyroid)

#### Pathology characteristics (graded by MRI or arthro CT)

- Tear location (posterolateral / anterosuperior)
- Size of tear (small (<1 cm), medium (1–3 cm), large (3–5 cm), or massive (>5 cm))
  - Size in the saggital oblique plane
- Fatty infiltration (Goutallier 0 - 4)
- Muscle atrophy as graded by tangent sign (yes / no)
- Tendon retraction (Patte 1 - 3)

#### Surgical Technique

- Single row (yes / no)
- Double row (yes / no)
- Suture bridge (yes no)
- Performing surgeon (surgeon / resident / fellow)

#### Rehabilitation protocol

- Timing of active mobilization (<6wks ≥ 6wks)

#### Add-on Intervention

- 1
- 2
- 3 ○ Biceps tenotomy/tenodesis (yes / no)
- 4 ○ Bone marrow stimulation by microfracturing footprint (yes/no)
- 5 ○ Steroid injections within year prior to surgery (0 / 1 / ≥2 injections)
- 6 ○ Augmentation with subacromial inflatable device (yes/no)
- 7 ○ Augmentation/bridging with patches/scaffolds/extracellular matrices (yes/no)
- 8 ○ Local injectable biologics (yes/no) including:
- 9
  - 10       ▪ Platelet-rich plasma (P-PRP, L-PRP)
  - 11       ▪ Leukocyte and platelet-rich fibrin (L-PRF)
  - 12       ▪ Growth factors
  - 13       ▪ Cell therapy (bone marrow stem cells / BMAC MSCs)
- 14 ○ Systemic drugs - Statins (yes/no)
- 15 ○ Systemic drugs - Vitamin D supplementation (yes/no)
- 16 ○ Systemic drugs - Vitamin C supplementation (yes/no)
- 17 ○ Systemic drugs – NSAIDs from >6 weeks postop (yes/no)
- 18
- 19

### 20 Outcomes

- 21 ○ Retear at minimum 6 months (yes no)
- 22 ○ Type of retear (Sugaya 1-5)
- 23 ○ Adverse event
- 24
  - 25       ▪ None/mild (none reported) / Moderate/severe (reported adverse event)
  - 26       ▪ Type of adverse event (Infection/revision/stiffness/other)
- 27 ○ PROMS
- 28
  - 29       ▪ Type of PROM
  - 30       ▪ Time of measurement (in days from surgery)
  - 31       ▪ Consistency of PROM (yes/no)
  - 32
    - 33               • *Will be seperately formulated per PROM based on MCID*
    - 34               • *As the calculation of this variable will be greatly dependent on which*
    - 35               • *PROMS and follow-up duration will be submitted by co-authors, we prefer*
    - 36               • *to receive 'raw' data.*
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# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-063673.R2
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Date Submitted by the Author:	04-Jan-2023
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<b>Primary Subject Heading</b>:	Surgery
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Keywords:	ORTHOPAEDIC & TRAUMA SURGERY, Shoulder < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic & trauma surgery < SURGERY

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Manuscripts



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3 **1 Developing a machine learning algorithm to predict probability of retear and functional outcomes in**  
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5 **2 patients undergoing rotator cuff repair surgery: protocol for a retrospective, multicenter study**  
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8 3 Laurens J. H. Allaart<sup>1,2</sup>, Sanne H. van Spanning<sup>2,3</sup>, Laurent Lafosse<sup>1</sup>, Thibault Lafosse<sup>1</sup>, Alexandre  
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24 31 **Keywords:** Rotator Cuff Tear, Rotator Cuff Repair, Retear, Machine Learning Algorithm, Artificial  
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3 36 **ABSTRACT**  
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6 37 **Introduction:** The effectiveness of rotator cuff tear repair surgery is influenced by multiple patient-  
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8 38 related, pathology-centered and technical factors, which is thought to contribute to the reported retear  
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10 39 rates between 17 and 94%. Adequate patient selection is thought to be essential in reaching satisfactory  
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12 40 results. However, no clear consensus has been reached on which factors are most predictive of  
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14 41 successful surgery. A clinical decision tool that encompassed all aspects is still to be made. Artificial  
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16 42 Intelligence (AI) and machine learning algorithms use complex self-learning models that can be used to  
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18 43 make patient-specific decision-making tools. The aim of this study is to develop and train an algorithm  
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20 44 that can be used as an online available clinical prediction tool, to predict the risk of retear in patients  
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22 45 undergoing rotator cuff repair.  
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27 46 **Methods and analysis:** This is a retrospective, multicenter, cohort study using pooled individual patient  
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29 47 data from multiple studies of patients who have undergone rotator cuff repair and were evaluated by  
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31 48 advanced imaging for healing at a minimum of 6 months after surgery. This study consists of two parts.  
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33 49 Part one: collecting all potential factors that might influence retear risks from retrospective multicenter  
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35 50 data, aiming to include >1000 patients worldwide. Part two: combining all influencing factors into a  
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37 51 model that can clinically be used as a prediction tool using machine learning.  
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41 52 **Ethics and dissemination:** For safe multicenter data exchange and analysis, our Machine Learning  
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43 53 Consortium adheres to the World Health Organization (WHO) regulation "Policy on Use and Sharing of  
44  
45 54 Data Collected by WHO in Member States Outside the Context of Public Health Emergencies". The study  
46  
47 55 results will be disseminated through publication in a peer-reviewed journal. Institutional Review Board  
48  
49 56 approval does not apply to the current study protocol.  
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3 58 **ARTICLE SUMMARY**  
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6 59 **Strengths and limitations of this study**  
7

8 60 - This study aims to calculate a patient-specific retear-chance after rotator cuff repair surgery.  
9

10 61 - Creating an online-available tool that predicts retear chances can help both medical  
11  
12 professionals and patients in clinical decision-making on rotator cuff repair surgery.  
13 62

14  
15 63 - Included data will be gathered from previously published databases of all authors included in the  
16  
17 Machine Learning Consortium, aiming to include data from over 1000 patients.  
18 64

19 65 - This study does have the limitation of being retrospective and therefore the study is dependent  
20  
21 on the recordkeeping of each individual hospital.  
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## 67 INTRODUCTION

68 Despite technical advances of rotator cuff repair, the rate of unhealed or re-torn rotator cuff tears  
69 remains high, with percentages ranging between 10 and 94% (1). A myriad of patient-related (2),  
70 pathology-centered(3) and technical factors(4) influence this adverse outcome.

71 Patient selection is thought to be essential, however there is no consensus on which of the numerous  
72 potentially influential factors are most important for the prediction of satisfactory postoperative results  
73 (5). Furthermore, the value of preoperative optimization of potential patient-related influential factors  
74 including comorbidities, metabolic deficiencies and intoxications remains questionable. The increasing  
75 worldwide interest in these factors is confirmed by development of preoperative screening and  
76 optimization programs aiming for smoking cessation, diabetes control, use of statins in hyperlipidemia  
77 and vitamin D deficiency supplementing (2,6). However, the majority of shoulder surgeons seems to limit  
78 decision-making to more basic, previously established predictive factors including age, functional  
79 demand and pathology-specific grading. Despite the many different classification systems that have been  
80 developed to facilitate decision making, a patient specific decision tool is still lacking (7,8). This, in  
81 combination with the fact that existing research commonly evaluates a single treatment option between  
82 homogenic groups, makes it almost impossible for surgeons to preoperatively indicate a reliable chance  
83 of satisfactory results.

84 Artificial intelligence and machine learning (ML) is believed to facilitate a more patient-specific approach  
85 and will allow us to move to the next level of evidence-based medicine: personalized patient-care.

86 Clinical prediction tools, incorporating patient specific factors to predict outcome probabilities will  
87 provide guidance to both clinicians and patients (9,10). Within orthopedic (oncology) surgery, prediction  
88 tools based on ML algorithms, have already been successfully implemented to predict patient specific 5-  
89 year survival in patients with chondrosarcoma (11). Furthermore, based on a series of 422 patients

1  
2  
3 90 undergoing lumbar discectomy, Staartjes et al. demonstrated deep learning algorithms to be superior to  
4  
5 91 standard regression models in predicting patient-reported outcome measures (PROMs)(9).  
6  
7

## 8 92 **Aim of this study**

9

10  
11 93 The aim of this study is to develop and train a machine learning algorithm in order to create a clinical  
12  
13 94 prediction tool to be used in clinical practice by predicting retear-chance of the rotator cuff as well as  
14  
15 95 chance of clinical improvement based on preoperative patient data. The prediction tool will be free and  
16  
17 96 online available.  
18  
19

## 20 21 97 **METHODS AND ANALYSIS**

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23  
24 98 This is a retrospective, multicenter, cohort study.

25  
26  
27 99 The primary and secondary outcome measures will be implemented as features for the prediction  
28  
29 100 algorithm.

### 30 31 101 Primary outcome measures

32  
33

- 34 102 - Rotator cuff retear rates at minimum 6 months follow-up as measured on magnetic resonance  
35  
36 103 imaging, arthro-CT and/or ultrasound (yes vs no, defined by Sugaya grade 1-3 as no retear and  
37  
38 104 grade 4-5 as retear (12)).  
39  
40  
41 105 - Enduring satisfactory functional outcome defined as achievement (yes vs no) and maintenance  
42  
43 106 (yes vs no) of the PROM-specific minimal clinical important difference (MCID) (13) in numeric  
44  
45 107 rating scales of PROMs from baseline at 2-5 years follow-up after repair (PROMs include the  
46  
47 108 Constant-Murley score, ASES, UCLA, OSS, WORC, DASH).  
48  
49  
50

### 51 109 Secondary outcome measures

52  
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- 54 110 - Adverse events graded as the possibility of none/minor vs moderate/severe complication as  
55  
56 111 defined in accordance to Felsch et al. (14). Adverse events classify as moderate/severe from  
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60

1  
2  
3 112 Felsch class III onwards, which means other surgical or radiologic intervention was needed or  
4  
5 113 unexpected hospital admission was necessary. Adverse events will be differentiated into three  
6  
7 114 groups: infection, revision surgery or other.  
8  
9

## 10 115 **Model development**

11  
12  
13 116 The development of the prediction model will be performed based on the steps described by Steyerberg  
14  
15 117 et al (15):

- 16 118 1. Data collection
- 17  
18 119 2. Data inspection
- 19  
20 120 3. Coding of predictors
- 21  
22 121 4. Model specification
- 23  
24 122 5. Model estimation and performance
- 25  
26 123 6. Model validation
- 27  
28 124 7. Model presentation
- 29  
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31  
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### 35 125 **1. Data collection**

36  
37 126 Step one will involve contacting authors from previously published studies in order to collect and  
38  
39 127 combine their (raw) individual patient data into a central database. All randomized controlled trials  
40  
41 128 comparing any surgical technique, add-on biological intervention or rehabilitation protocols concerning  
42  
43 129 rotator cuff surgery will be included. In addition, cohorts evaluating risk factors of surgical techniques  
44  
45 130 after rotator cuff repair will be included. This retrospective review will therefore incorporate patients  
46  
47 131 with all types of tears and concomitant procedures (e.g. biceps tenodesis or tenotomy and  
48  
49 132 acromioclavicular resection). Exclusion criteria for all studies will be the lack of postoperative evaluation  
50  
51 133 by ultrasound, contrast-enhanced computed tomography or magnetic resonance imaging at minimally 6  
52  
53 134 months after surgery, or publication date from before 2005. Relevant studies will be identified using a  
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3 135 systematic approach primarily searching the online PubMed database according to the search terms  
4  
5 136 found in supplement 1. As there is no golden standard for sample size or power calculations for  
6  
7 137 prediction models, and we are fully dependent on contributed data, we aim to include at least 1000  
8  
9 138 patients worldwide (15).

## 139 **2. Problem definition and data inspection**

140 All contributed data sets will be formatted into one central database. As data is commonly collected in  
141 .csv (Microsoft Excel) or .sav (SPSS) files, formatting will be performed with the dplyr package for R  
142 software. All raw data of the different variables will be separately reviewed for inaccuracies and other  
143 defects. This process will focus on uniformization of possible inconsistencies in the collected data, for  
144 example follow-up times into a standardized format as 'days after surgery'. Categorical data will be  
145 translated into English or corrected for typographs. Continuous variables will be screened for outliers by  
146 visualization in the ggplot package. Impossible values or uninterpretable syntax errors will be excluded  
147 from the central database.

## 149 **3. Coding of predictors**

150 For each primary outcome, a logistic regression will be performed including all available variables in the  
151 central database to identify the variables with the highest predictive values. The data points available  
152 include patient demographic (sex, age), patient specific factors (BMI, dominance, sport/activity level,  
153 workers compensation), pathology specific factors (e.g. tear size and location), surgical technique and  
154 add-on interventions. For a complete overview of all variables see supplement 2. The variables with the  
155 highest predictive values will be used as the algorithms labels.

156



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2  
3 157 *Missing data*  
4  
5

6 158 As the main database will comprise data from multiple studies, we expect many cases of missing data.  
7

8 159 The approach to missing data will differ depending on the type of variable. Variables with less than 5%  
9

10 160 missing data will be replaced by imputation (16). Missing data on any surgical technique or add-on  
11

12 161 intervention is expectable as interventions outside the scope of a study would not be mentioned (or  
13

14 162 briefly mentioned in the exclusions part). Therefore, this kind of missing data will be transformed to 'No'.  
15

16 163 Overall availability of variables will be presented according to current guidelines (17). Any variances  
17

18 164 between hospitals will be reported.  
19  
20  
21

22 165 **4. Model specification**  
23  
24

25 166 *Algorithms to be trained*  
26  
27

28 167 Based on previous studies (18,19), the following algorithms are likely to result in accurate prediction  
29

30 168 models for our primary outcomes: 1) Bayes Point Machine 2) Boosted Decision Tree 3) Penalized  
31

32 169 Logistical Regression 4) Neural Network 5) Support Vector Machine. In order to recognize patterns  
33

34 170 related to each outcome, the machine learning algorithms will have to be trained separately for each  
35

36 171 outcome.  
37  
38  
39

40 172 **5. Model estimation and performance**  
41  
42

43 173 *Assessing the performance of the algorithms*  
44  
45

46 174 The performance of the ML-algorithms will be assessed and compared based on 1) model discrimination;  
47

48 175 2) calibration and 3) overall model performance (Brier Score) according to Steyerberg's structured  
49

50 176 'ABCD-methodology' for clinical prediction rules (15,20).  
51  
52

53 177 The model's predicted probability will be plotted against the actual observed probability to calculate  
54

55 178 calibration of a model. Perfect models will have calibration intercepts of 0, and calibration slopes of 1.27  
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3 179 The overall performance of the model will be assessed with the Brier-score. A perfect Brier score,  
4  
5 180 indicating total accuracy, is a score of 0. The lowest possible score is a Brier score of 1.26. Accuracy,  
6  
7 181 sensitivity, specificity and area under the ROC-curve will be measures for a model's ability to distinguish  
8  
9  
10 182 patients with the primary outcome from those without.

## 11 12 183 **6. Model validation**

### 13 14 15 184 *Internal validation*

16  
17  
18 185 Internal validation of our algorithms will be performed by 10-fold cross validation. This means that  
19  
20 186 instead of dividing the main data set into one training set and one testing set, this process will be 10  
21  
22 187 times randomly repeated and the results will be averaged. This has as main advantage that all individual  
23  
24 188 patient records are used as training and testing data simultaneously, which results in higher accuracy of  
25  
26  
27 189 predictions as well as lower chance of bias. The cross validation will be performed using the trainControl  
28  
29 190 function from the Caret library for R.

### 30 31 32 191 *External validation*

33  
34  
35 192 Before incorporating the best performing algorithm, we aim to have the algorithm externally validated.  
36  
37 193 The same performance metrics could be calculated as described above. However, this would involve  
38  
39 194 collaboration with partners that have adequate data and are willing to share. As no agreements currently  
40  
41 195 have been made, the external validation is outside the scope of this study.

## 42 43 44 196 **7. Model presentation**

45  
46  
47 197 The best performing algorithm will be deployed as an open-access probability calculator and used to  
48  
49 198 design a clinical decision rule. To simulate the clinical scenario to which a decision rule would be most  
50  
51 199 applicable, thresholds shall be selected based on patients with clinical symptoms of a re-tear or with an  
52  
53  
54 200 unsatisfactory functional outcome.

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3 201 **Patient and public involvement**  
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5

6 202 None.  
7  
8

9 203 **ETHICS AND DISSEMINATION**

10 204 For safe multicenter data exchange and analysis, our Machine Learning Consortium adheres to the World  
11  
12 205 Health Organization (WHO) regulation 'Policy on Use and Sharing of Data Collected by WHO in Member  
13  
14 206 States Outside the Context of Public Health Emergencies'.(21) As Institutional Review Board (IRB)  
15  
16 207 approval has been acquired for each of the included studies and data are anonymized as in conventional  
17  
18 208 meta-analyses, additional IRB approval is not required for the current study protocol. The technical  
19  
20 209 appendix, statistical code and final dataset will be published with the study results.  
21  
22  
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24

25 210 **CURRENT STATUS**

26  
27 211 The study has currently entered the data-collection phase, which is expected to last until March 2023.  
28  
29 212 Re-evaluation of the data using machine learning algorithms to predict outcomes will start in April 2023,  
30  
31 213 after which the algorithms can be externally validated. The expected time for study completion is by late  
32  
33 214 2023.  
34  
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36

37 215 **DISCUSSION**

38  
39 216 Due to the wide variety of pathological factors at the origin of rotator cuff tears and the numerous  
40  
41 217 surgical approaches to repair, optimal decision-making remains challenging. Smaller case series often  
42  
43 218 provide heterogeneous data on this topic, however the largest and most recent meta-analysis to date  
44  
45 219 including 2,611 patients with a mean follow-up of 25 months has somewhat demystified the matter.  
46  
47 220 Patients with a full-thickness rotator cuff re-rupture exhibited significantly lower functional outcome scores  
48  
49 221 and strength compared with patients with an intact or partially torn rotator cuff (22). This is  
50  
51 222 corroborated by the findings of rotator cuff repair with more than 10 years follow-up, showing clinical  
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53 223 superiority of structural tendon integrity in partial cuff tears (23–25). Progressive osteoarthritic changes  
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3 224 are significantly more common in patients with repair failures (24). The most recent randomized  
4  
5 225 controlled trial comparing surgical repair to conservative treatment for degenerative rotator cuff tears  
6  
7 226 showed that only operated patients without retear had an improvement exceeding the MCID in  
8  
9  
10 227 functional outcome at 1 year follow-up (26). Findings from the latest meta-analysis on this comparative  
11  
12 228 topic conclude that as the success rate of conservative treatment may be high, judicious selection of  
13  
14 229 patients who are most likely to benefit from surgery is key (27). It is extremely difficult to combine all  
15  
16 230 these factors into a clinical decision related to one specific patient. Creating a free online available  
17  
18 231 clinical prediction tool that takes all these factors into account will assist physicians in selecting which  
19  
20 232 patients with rotator cuff tears will benefit from a repair. In addition, the aimed size (more than 1000  
21  
22 233 patients) of the database that will be used to design and train the prediction tool might provide new  
23  
24 234 insights on which biological or biomechanical factors influence outcomes after rotator cuff repair the  
25  
26 235 most. Awareness of these factors would be the essential first step to incorporating them in future  
27  
28 236 treatment strategies and eventually improving outcomes. The main limitation of this study is that it is a  
29  
30 237 retrospective, multicenter study. This means this study is dependent on the quality of recordkeeping in  
31  
32 238 the different participating hospitals. This may lead to variance in recorded variables and therefore  
33  
34 239 missing data.  
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42 241 \*\* \*\* \*\*

#### 45 242 **CONTRIBUTORS**

48 243 Laurens J.H. Allaart, Sanne H. van Spanning, Geert Alexander Buijze and Michel P.J van den Bekerom  
49  
50 244 contributed to the conception, overall design and planning of the study. Laurent A.M. Hendrickx and Job  
51  
52 245 N. Doornberg contributed to the conception and design of the methods section, primarily focussing on  
53  
54 246 the machine learning section and data analysis. Alexander Lädermann, George S Athwal, Thibault Lafosse  
55  
56  
57  
58  
59  
60

1  
2  
3 247 and Laurent Lafosse contributed to the design of the methods section and primarily focussed on how the  
4  
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6  
7 249 Buijze and Michel P.J. van den Bekerom contributed to writing the protocol. All authors revised this  
8  
9  
10 250 version of the protocol and gave final approval for it to be published. All authors ensure that questions  
11  
12 251 related to the accuracy or integrity of any part of this protocol are appropriately investigated and  
13  
14 252 resolved.

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21  
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### 25 256 **COMPETING INTERESTS**

26  
27  
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29  
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31  
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33  
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48  
49  
50 266 The Effect of Risk Factors, Surgical Technique and Biomodulation on Tendon Healing  
51  
52  
53 267 after Rotator Cuff Repair'.

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- 51 339

1  
2  
3 #1 subject

4 Rotator cuff tear/ injury

5  
6 **(rotator[tiab] AND cuff[tiab] AND injur\*[tiab])**

7 **OR**

8  
9 **(rotator[tiab] AND cuff[tiab] AND tear\*[tiab])**

10 **OR**

11  
12 **(rotator[tiab] AND cuff[tiab] AND repair\*[tiab])**

13 **OR**

14  
15 **(rotator[tiab] AND cuff[tiab] AND surg\*[tiab])**

16 **OR**

17 **"Rotator Cuff Injuries"[Mesh]**

18  
19 #2.1 Intervention (RCT)

20 Repair

21  
22 #2.2 Intervention (Cohort)

23 Repair

24  
25 #3 Outcome

26 Retear rate measured by MRI ultrasound or arthro CT

27  
28 **(Retear[tiab] OR (re-tear)[tiab] OR healing[tiab])**

29 **OR**

30 **("Magnetic Resonance Imaging"[Mesh] OR "MRI" OR "magnetic resonance"**

31 **OR**

32 **ultraso\*[tiab] OR "Ultrasonography"[Mesh]**

33 **OR**

34 **"Arthrography"[Mesh] OR arthrography[tiab])**

35  
36  
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39  
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43  
44  
45  
46 Search: **((Retear[tiab] OR re-tear[tiab] OR healing[tiab]) OR ("Magnetic Resonance**  
47 **Imaging"[Mesh] OR "MRI" OR "magnetic resonance" OR ultraso\*[tiab] OR**  
48 **"Ultrasonography"[Mesh] OR "Arthrography"[Mesh] OR arthrography[tiab]) ) AND**  
49 **((rotator[tiab] AND cuff[tiab] AND injur\*[tiab]) OR (rotator[tiab] AND cuff[tiab] AND**  
50 **tear\*[tiab]) OR (rotator[tiab] AND cuff[tiab] AND repair\*[tiab]) OR (rotator[tiab] AND**  
51 **cuff[tiab] AND surg\*[tiab]) OR "Rotator Cuff Injuries"[Mesh]) Filters: Clinical Trial,**  
52 **Randomized Controlled Trial Sort by: Most Recent**  
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We will collect the following potential risk factors from the electronic medical records. The variables are mostly binary to make them compatible for all machine learning algorithms. Cut-off values will be used for the non-binary values. In case of doubt, overlap or less specific grouping than in this database, variables will be rounded up.

#### Patient characteristics

- Identification number
- Date of birth
- Sex
- Dominant side (yes/no)
- Chronicity of tear (<6 weeks / >6weeks)
  - Time from trauma to 1<sup>st</sup> treatment day
- ASA classification (1-4)
- Sport/activity level
- Receiving workers compensation (yes/no)

#### Biological factors

- Obesity (BMI <30 / ≥30)
- Cardiovascular disease incl. hypertension (yes / no)
- Smoking history (current smoker / non-smoker)
- Diabetes (yes/no; insulin dependent yes/no)
- Osteoporosis (yes/no)
- Hyperlipidemia (yes/no)
- Hypercholesterolemia (yes/no)
- Vitamin D deficiency (yes/no)
- NSAID use (yes/no)
- Thyroid dysfunction (no disease / hypothyroid / hyperthyroid)

#### Pathology characteristics (graded by MRI or arthro CT)

- Tear location (posterolateral / anterosuperior)
- Size of tear (small (<1 cm), medium (1–3 cm), large (3–5 cm), or massive (>5 cm))
  - Size in the saggital oblique plane
- Fatty infiltration (Goutallier 0 - 4)
- Muscle atrophy as graded by tangent sign (yes / no)
- Tendon retraction (Patte 1 - 3)

#### Surgical Technique

- Single row (yes / no)
- Double row (yes / no)
- Suture bridge (yes no)
- Performing surgeon (surgeon / resident / fellow)

#### Rehabilitation protocol

- Timing of active mobilization (<6wks ≥ 6wks)

#### Add-on Intervention

- 1
- 2
- 3 ○ Biceps tenotomy/tenodesis (yes / no)
- 4 ○ Bone marrow stimulation by microfracturing footprint (yes/no)
- 5 ○ Steroid injections within year prior to surgery (0 / 1 / ≥2 injections)
- 6 ○ Augmentation with subacromial inflatable device (yes/no)
- 7 ○ Augmentation/bridging with patches/scaffolds/extracellular matrices (yes/no)
- 8 ○ Local injectable biologics (yes/no) including:
  - 9     ▪ Platelet-rich plasma (P-PRP, L-PRP)
  - 10    ▪ Leukocyte and platelet-rich fibrin (L-PRF)
  - 11    ▪ Growth factors
  - 12    ▪ Cell therapy (bone marrow stem cells / BMAC MSCs)
- 13 ○ Systemic drugs - Statins (yes/no)
- 14 ○ Systemic drugs - Vitamin D supplementation (yes/no)
- 15 ○ Systemic drugs - Vitamin C supplementation (yes/no)
- 16 ○ Systemic drugs – NSAIDs from >6 weeks postop (yes/no)
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- 19

### 20 Outcomes

- 21 ○ Retear at minimum 6 months (yes no)
- 22 ○ Type of retear (Sugaya 1-5)
- 23 ○ Adverse event
  - 24     ▪ None/mild (none reported) / Moderate/severe (reported adverse event)
  - 25     ▪ Type of adverse event (Infection/revision/stiffness/other)
- 26 ○ PROMS
  - 27     ▪ Type of PROM
  - 28     ▪ Time of measurement (in days from surgery)
  - 29     ▪ Consistency of PROM (yes/no)
    - 30         • *Will be seperately formulated per PROM based on MCID*
    - 31         • *improvement/consistency*
    - 32         • *As the calculation of this variable will be greatly dependent on which*
    - 33         • *PROMS and follow-up duration will be submitted by co-authors, we prefer*
    - 34         • *to receive 'raw' data.*
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