PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical Outcomes and Cost-Utility of Rotator Cuff Repair Surgery by Open and Arthroscopic Techniques: Study Protocol for a Randomized Clinical Trial.
AUTHORS	Pierami, Rafael; Antonioli, Eliane; Oliveira, Isadora; Castro, Isabela; Manente, Felipe; Fairbanks, Paula; Carrera, Eduardo; Matsumura, Bruno; Lenza, Mario

VERSION 1 – REVIEW

REVIEWER	Richard Craig University of Oxford, UK
REVIEW RETURNED	28-Aug-2020

GENERAL COMMENTS	Thank you for inviting me to review this protocol. I wish the authors well with the conduct of their study and look forward to the results. The typeface used by the authors is very difficult to read quickly. Please could the editors encourage the authors to submit any revisions in a more standard font. The authors report the protocol for a randomised controlled trial that seeks to answer the question of which surgical treatment is most effective and cost-effective for the management of rotator cuff tears (arthroscopic or open). Could the authors please clarify what the primary purpose of the study is please. The study title refers to “cost-utility”, but the primary outcome is a patient reported and surgeon measured shoulder score. I would recommend that a statistical and health economic reviewer see the manuscript. The study is relatively small and powered on the Constant Murley Score. I suspect that it will be large enough to address the goal of comparing cost-utility between the different treatments. Why did the authors choose to use the Constant Murley Score? Whilst it is widespread and accepted in shoulder surgery, it is at more immediate risk of bias than many other purely patient recorded scores due to the surgeon measured elements of the scoring system. Please be more explicit about the criteria that are used for inclusion of patients, specifically the type of imaging that will be used preoperatively to confirm the diagnosis. Please report which research ethics committee approved the study and any reference number. Line 68: Misspelling – “Strenghts”

	Line 72: “techinique” Line 103: Consider avoid use of the term “injuries” – the pathophysiology of most rotator cuff tears is not thought to be traumatic in origin. Line 109: There are a number of national guidelines available recommending thresholds for surgical intervention. Consider referencing your statement. Line 112: Imaging may assist in planning of surgical treatment, but this sentence needs qualifying. It has been shown that ultrasound of the rotator cuff is highly operator dependent compared to a gold standard of arthroscopic assessment. Line 121: “should be treated surgically” – Surgical treatments are something that surgeons offer to patients. The word “should” is too strong here Line 137: I would again discourage the use of the word “injury” (and throughout the protocol where mentioned) Line 218: Please could you explain the randomisation process more clearly. You refer here to “variables”. Are these variables across which the randomisation with be stratified, or variables for which you will adjust in the analysis of results? Line 250: It is interesting that the surgery will be performed in different positions and that the type of repair will be left to the surgeon preference. There is a potentially missed opportunity her to provide further standardisation between the study arms and reduce sources of bias. Line 324: What is the predetermined study endpoint? 6 weeks/24 weeks/48 weeks? Same line – are there any plans to reevaluate patients at longer follow-up: ?5 years Line 422: Are there any known adverse events form the surgery that the investigators have specified for reporting? Line 449: Please describe the formal method of protecting the patient data, or remove this statement.

REVIEWER	Efthymios Iliopoulos Brighton & Sussex University Hospitals
REVIEW RETURNED	05-Sep-2020

GENERAL COMMENTS	Thank you very much for the opportunity to review this interesting study protocol. The authors have made a significant effort, planning, developing and presenting their study protocol. I present my comments in a point-by point manner, with the view of enhancing the manuscript. Title: The primary outcome of the study as stated in the abstract and the body of the manuscript is the final Constant-Murley score, which is a functional score. The present title of the protocol does not correspond to that, instead is presented as the cost-utility as the

	primary outcome, which in the text is presented as a secondary outcome. The title of the protocol should depict this. Abstract Line 31: the phrase 'shoulder girdle' is not usually used, consider changing it. Article Summary Lines 63-64: The first point in the article summary is a general statement and not something derived from the study, consider amending it. Background Line 79: The authors are using data from almost 20 years. Consider using more recent data. Lines 95-99: There is a duplication on the information given, consider shortening this section to avoid duplications. Line 103: In this paragraph the association of the RC tears with the age should be discussed as well. Lines 109-122: These two paragraphs are too long and they are not directly relevant to the point, the authors try to make. Consider shortening this section. Line 123-135: At this paragraph the authors present some other studies which have the same design and outcomes with the present study. It is not clear what exactly is the novelty of this particular study. Are the authors just duplicating other studies or trying to tackle the issue from another angle? Or trying to investigate the cost-effectiveness in their country? Inclusion criteria Lines 189-190: Consider changing the word 'injury' with the word 'tear', also consider rephrasing the first sentence of the paragraph to make it more clear for the reader. Lines 192-193: This should be in the exclusion criteria section. Patient and public involvement Line 242: It is stated that there is 'no patient involved', what is this referring to? The subjects of the study are patients. Intervention methods Line 252: the word range has been used twice. Lines 252-3: the phrase 'asepsis, antisepsis' is not usually used, consider rephrasing. Line 260: Please add the company and country of origin of the metal anchors intended to be used. Add this info in brackets. Lines 269-270: Same comment about the asepsis etc. Also the phrase 'establishment of arthroscopic portals' is more appropriate. Outcomes assessment Line 301: please add in brackets the company and country of origin of REDCap. Line 322: The authors should add the information about what will happen if they fail to retrieve the questionnaires, are they planning to exclude these patients? Primary outcome & Secondary outcome The authors have different punctuation in the three paragraphs when they describe the timing of the data collection. The last one (lines 347-8) is the most appropriate.

	Line 329: The goniometer which will be used is an electronic or an analog one? This info should be included. Line 332: The reference should be added again at the end of the paragraph. Lines 342-345: What will be the range of this scale? Line 357: The VAS scale does not measured in centimetres. The 'cm' should be removed. Lines 361-362: This should be moved in the next paragraph. Line 371: Consider amending the first sentence, as it doesn't make sense. Line 380: Why the 5% discount will be applied? Where this is based on? Lines 381-2: The two techniques have different surgical costs (eg. arthroscopic set etc). These should be mentioned in detail in this section. Line 383: Change the word 'absenteeism' with 'absence' or 'loss of working hours' or something similar. Line 410: Consider changing the word 'numerical' to 'continuous variables' Lines 419-420: Please add in brackets the company and the country of origin for SPSS, intended to be used. Line 448: Consider changing the word 'reversed' with 'resolve' Discussion Line 487: Try to avoid words as 'elegant' in the manuscript. Line 515: A typo mistake on VAS.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Richard Craig
Institution and Country: University of Oxford, UK
Please state any competing interests or state ‘None declared’: None declared

Thank you for inviting me to review this protocol. I wish the authors well with the conduct of their study and look forward to the results.
Answer: Thank you for your careful review and help with the manuscript.

1. The typeface used by the authors is very difficult to read quickly. Please could the editors encourage the authors to submit any revisions in a more standard font.
Answer: As suggested, we changed to standard font (Times New Roman, 12).

2. The authors report the protocol for a randomised controlled trial that seeks to answer the question of which surgical treatment is most effective and cost-effective for the management of rotator cuff tears (arthroscopic or open).
Could the authors please clarify what the primary purpose of the study is please. The study title refers to “cost-utility”, but the primary outcome is a patient reported and surgeon measured shoulder score. I would recommend that a statistical and health economic reviewer see the manuscript. The study is relatively small and powered on the Constant Murley Score. I suspect that it will be large enough to address the goal of comparing cost-utility between the different treatments.
Answer: The primary purpose of the study is to determine which repair method has the better cost-utility ratio. Also, it will provide clinical outcomes about both methods of rotator cuff repair. A statistical

and a health economic reviewer are already part of the team, since its beginning. They helped to develop the project and calculate the sample size needed to achieve the power needed to detect a significant difference on the outcomes. Also, they will help us to evaluate the data obtained.

3. Why did the authors choose to use the Constant Murley Score? Whilst it is widespread and accepted in shoulder surgery, it is at more immediate risk of bias than many other purely patient recorded scores due to the surgeon measured elements of the scoring system.
Answer: The constant-Murley score is one of the most commonly used scores on shoulder scoring system and is considered the gold-standard in Europe(Angst et al. 2011)(Constant et al. 2008). It is reliable for detection of shoulder improvement after surgical procedures and its strong correlation with shoulder specific diseases, especially rotator cuff, and reliability makes it a good score system for a clinical research.

4. Please be more explicit about the criteria that are used for inclusion of patients, specifically the type of imaging that will be used preoperatively to confirm the diagnosis.
Answer: All patients will have the diagnostic confirmed by MRI.

5. Please report which research ethics committee approved the study and any reference number.
Answer: As suggested by the reviewers, this information was given at the end of the protocol

6. Line 68: Misspelling – “Strenghts”
Answer: The word “strengths” was revised.

7. Line 72: “techinique”
Answer: The word “technique” was revised.

8. Line 103: Consider avoid use of the term “injuries” – the pathophysiology of most rotator cuff tears is not thought to be traumatic in origin.
Answer: As suggested by reviewer, the word “injuries” was changed to “lesion” or “tear” throughout the manuscript

9. Line 109: There are a number of national guidelines available recommending thresholds for surgical intervention. Consider referencing your statement.
Answer: As suggested by reviewer, we included the information about the guidelines and rephrased the paragraph, so it is more direct and concise. The text was changed as follow:
“Treatment of rotator cuff lesion depends on the type of tear, the patient's functional capacity, age, and the presence of symptoms. In general, tendon degeneration and partial tears are treated non-surgically, with physiotherapy, injections and analgesic medications. Complete and incomplete tears that did not respond well to conservative treatment, however, might be treated surgically”

Line 112: Imaging may assist in planning of surgical treatment, but this sentence needs qualifying. It has been shown that ultrasound of the rotator cuff is highly operator dependent compared to a gold standard of arthroscopic assessment.
Answer: we decided to remove e rephrase this sentence of the paragraph.

Line 121: “should be treated surgically” – Surgical treatments are something that surgeons offer to patients. The word “should” is too strong here
Answer: We agree with the reviewer that the treatment is an option, then we changed the word “should” to “might”

Line 137: I would again discourage the use of the word “injury” (and throughout the protocol where mentioned).
Answer: As suggested by reviewer, all occurrences of “injury” were changed to “lesion” or “tear”.

Line 218: Please could you explain the randomization process more clearly. You refer here to “variables”. Are these variables across which the randomisation with be stratified, or variables for which you will adjust in the analysis of results?
Answer: The randomization process will use the variables smoking, the size of the lesion 3 cm) and diabetes to stratify patients.
We included the sentence to clarify this information:. “A stratified randomization will be performed using the following variables (strata): smoking (yes or no), the size of the lesion (≤ 3 cm or > 3 cm) and diabetes (present or absent)”

Line 250: It is interesting that the surgery will be performed in different positions and that the type of repair will be left to the surgeon preference. There is a potentially missed opportunity her to provide further standardisation between the study arms and reduce sources of bias.
Answer: Since a great number of recent papers, including systematic reviews, showed no difference between types of repair, we preferred to leave to surgeons the type of repair they are used to and are comfortable performing; the position of the patient- beach chair or lateral decubitus- makes no difference in rotator cuff repair.

Line 324: What is the predetermined study endpoint? 6 weeks/24 weeks/48 weeks?
Answer: The predetermined endpoint to cost analysis is 48 weeks; however, the clinical outcomes will be also assessed at 6 and 24 weeks.

Same line – are there any plans to reevaluate patients at longer follow-up: ?5 years
Answer: This study aims to follow patients for 48 weeks. We thank the reviewer's suggestion and we will consider it to a new study, which may be a continuation of this.

Line 422: Are there any known adverse events form the surgery that the investigators have specified for reporting?
Answer: This is a very secure procedure, with a very low adverse events rate; if any adverse events occur, it will, for sure, be reportedly. What we see of great importance is the evaluation of rotator cuff healing and re-tear rate, since this is not well known in the literature.

Line 449: Please describe the formal method of protecting the patient data or remove this statement.
Answer: The data will be managed, stored, and protected by REDCAP software. Only the main investigator will have access to all data during the trial period.

Reviewer: 2
Reviewer Name: Efthymios Iliopoulos
Institution and Country: Brighton & Sussex University Hospitals, UK
Please state any competing interests or state ‘None declared’: None Declared

Thank you very much for the opportunity to review this interesting study protocol. The authors have made a significant effort, planning, developing and presenting their study protocol. I present my comments in a point-by point manner, with the view of enhancing the manuscript.
Answer: Thank you for your careful review and help with the manuscript.

Title:
The primary outcome of the study as stated in the abstract and the body of the manuscript is the final Constant-Murley score, which is a functional score. The present title of the protocol does not correspond to that, instead is presented as the cost-utility as the primary outcome, which in the text is presented as a secondary outcome.
The title of the protocol should depict this.
Answer: We evaluated the title and adapted it to: Clinical Outcomes and Cost-Utility of Rotator Cuff Repair Surgery by Open and Arthroscopic Techniques: Study Protocol for a Randomized Clinical Trial.

Abstract
Line 31: the phrase 'shoulder girdle' is not usually used, consider changing it.
Answer: As suggested by reviewer, we exclude the word “girdle” of the sentence.

Article Summary
Lines 63-64: The first point in the article summary is a general statement and not something derived from the study, consider amending it.
Answer: As noted by the reviewer and the editor suggested, we exclude this information.

Background
Line 79: The authors are using data from almost 20 years. Consider using more recent data.
Answer: The paragraph was reformulated to be more precise and concise; also, more recent data was included. The changes were made as follows:
“Musculoskeletal injuries are a major cost to the healthcare system. North American data estimate that approximately 4.5 million patients annually seek medical attention due to shoulder pain; of these, two million have some symptoms related to the rotator cuff. About 250,000 rotator cuff repair surgeries are performed annually in the United States of America (US), and with the continued increase in life expectancy and aging, there is a tendency to increase this number[1][2][3]. An evaluation of the primary health care system in Cambridge, United Kingdom, showed that the average frequency of shoulder pain was 9.5 per 1,000 individuals [4]. Of these, 86% had rotator cuff tendinopathy.”

Lines 95-99: There is a duplication on the information given, consider shortening this section to avoid duplications.
Answer: Thanks for the suggestions, the sentence was adapted to:
“The rotator cuff is a group of four muscles: subscapularis, supraspinatus, infraspinatus, and teres

minor, and their tendons, which act to stabilize the shoulder and allow for its extensive range of motion."

Line 103: In this paragraph the association of the RC tears with the age should be discussed as well.
Answer: As suggested by reviewer, we included the information about the association of RC tears and aged in the sentence:
"Its etiology is multifactorial and the main factors associated with tears are tendon degeneration related to aging, trauma, tendon insertion hipovascularity and genetic factors[6][7][8]. Since most lesions are caused by wear and degeneration related to aging, people over 40 years are at great risk"

Lines 109-122: These two paragraphs are too long and they are not directly relevant to the point, the authors try to make. Consider shortening this section.
Answer: As suggested by reviewer, the paragraphs was changed to:
"Treatment of rotator cuff lesion depends on the type of tear, the patient's functional capacity, age, and the presence of symptoms. In general, tendon degeneration and partial tears are treated non-surgically, with physiotherapy, injections and analgesic medications. Complete and incomplete tears that did not respond well to conservative treatment, however, might be treated surgically [12], [18]–[20][3][21][22]"

Line 123-135: At this paragraph the authors present some other studies which have the same design and outcomes with the present study. It is not clear what exactly is the novelty of this particular study. Are the authors just duplicating other studies or trying to tackle the issue from another angle? Or trying to investigate the cost-effectiveness in their country?
Answer: We are not duplicating existing studies, but trying to determine and prove that the open rotator cuff repair is still a viable, reliable and cost-effective method and should not be forgotten. The statement was rephrased as follows:
"To date, no study in our country has assessed the comparison of the cost-utility of the two techniques; considering that the open technique is being left behind, is important to determine if it remains a viable, reliable and cost-effective option for the treatment of rotator cuff tears."

Inclusion criteria
Lines 189-190: Consider changing the word 'injury' with the word 'tear', also consider rephrasing the first sentence of the paragraph to make it clearer for the reader.
Answer: As suggested by reviewer, all occurrences of "injury" were changed to "lesion" or "tear". The paragraph was rephrased, as follows:
"All patients eighteen years of age or older, presenting with complete rotator cuff tear or a partial rotator cuff tear of at least 50% of tendon thickness, with symptoms (pain and/or weakness), where conservative therapy failed will be included. The tendon tear will be confirmed by a Magnetic Resonance Imaging (MRI)."

Lines 192-193: This should be in the exclusion criteria section.
Answer: Thanks for the suggestions, as mentioned above, the paragraph was adapted.

Patient and public involvement
Line 242: It is stated that there is 'no patient involved', what is this referring to? The subjects of the study are patients.
Answer: Patients were not involved in the design and development of the protocol. We realized that this information was missing, then included the paragraph:
“The patients nor the public were involved on the design and development of this study. Their participation will first occur with the contact between the surgeon and patient, time which they will be informed about the study and will decide to participate or not. At this time, they will be informed about the purpose and importance of it. At all times during the follow-up the patients will be able to enquiry the researchers and surgeons about the project and to make suggestions and complaints about it. All the outcomes measures will be self-reported. In case of doubts from the patients, they will be assisted by one member of the research team.”

Intervention methods
Line 252: the word range has been used twice.
Answer: Thanks for pointing out this error, we have deleted the word “range” at the end of the sentence.

Lines 252-3: the phrase 'asepsis, antisepsis' is not usually used, consider rephrasing.
Answer: As suggested by reviewer the sentence was change to:
“After standard patient preparation, an anterolateral incision will be made in the shoulder; the deltoid muscle belly will be gently divided along its fibers until exposure of the subdeltoid / subacromial bursa, which will be partially excised for exposure of the subacromial space and rotator cuff tendons.”

Line 260: Please add the company and country of origin of the metal anchors intended to be used. Add this info in brackets.
Answer: The information about the metal anchors was added at the paragraph:
“(“Super Revo”-CONMED, USA)”

Lines 269-270: Same comment about the asepsis etc. Also, the phrase 'establishment of arthroscopic portals' is more appropriate.
Answer: As suggested by reviewer the sentence was adapted:
“After standard patient preparation, a posterolateral incision will be made in the shoulder for optic introduction, with a 50mmHg pressure pump and a 0.90 flow, and inspection of the glenohumeral joint. After establishment of all required arthroscopic portal.”

Outcomes assessment
Line 301: please add in brackets the company and country of origin of REDCap.
Answer: The information of REDCap was included:
“(“Vanderbilt University, Nashville, Tennessee, USA”)”

Line 322: The authors should add the information about what will happen if they fail to retrieve the questionnaires, are they planning to exclude these patients?
Answer: The statistical analyses of this project were developed considering the possibility of follow-up

loss; so, following the intention to treat principle, we added the following information:
“If the patient became incommunicable, we will consider a lost follow-up scenario, where, in accordance with the intention to treat principle, appropriate statistical methods for data analysis, that consider unbalanced data and loss of follow-up, such as Generalized Estimating Equation Model (GEE), will consider all patients observations, even if they fail in some moment. Thereby, these patients will not be excluded and all data will be considered. “

Primary outcome & Secondary outcome
The authors have different punctuation in the three paragraphs when they describe the timing of the data collection. The last one (lines 347-8) is the most appropriate.
Answer: Thanks for suggestions, the timing of the data collection was standardized to:
“preoperatively and at 6, 24 and 48 weeks after the procedure”.

Line 329: The goniometer which will be used is an electronic or an analog one? This info should be included.
Answer: The range of motion will be measure with an analogic goniometer, the information was included in the sentence.
“Research assistants (not blinded to the study aim) will ask the patients to fill in the validated CM form for the Portuguese language and measure the range of motion with an analogic goniometer.”

Line 332: The reference should be added again at the end of the paragraph.
Answer: As suggested by reviewer, the reference was added.

Lines 342-345: What will be the range of this scale?
Answer: This EuroQoL scare reflects the patient’s judgement about his own state of health. It ranges from 0 (“the worst imaginable state of health”) to 100 (“the best imaginable state of health”). The information was added as follows:
“…the EuroQol-5D-3L has a visual analog scale where the participant assigns a value between 0 and 100 to his or her own health condition, where 100 means “the best imaginable health status” or “the best health state you can imagine” and 0 means “the worst imaginable health state” or “the worst health state you can imagine”. This is used to obtain a respondent’s stated preference values, not to record their own health state.”

Line 357: The VAS scale does not measure in centimetres. The 'cm' should be removed.
Answer: As suggested by reviewer the word “cm” was excluded.

Lines 361-362: This should be moved in the next paragraph.
Answer: As suggested by reviewer the sentence was moved for the next paragraph.

Line 371: Consider amending the first sentence, as it doesn't make sense.
Answer: The sentence was adapted to:
“At the final follow-up (forty-eight weeks), the integrity and healing of repaired rotator cuff will be assessed through Magnetic Resonance Imaging (MRI).”

Line 380: Why the 5% discount will be applied? Where this is based on?
Answer: Usually in longitudinal studies, it is applied a discount rate per year to update the values which may change during the study period. The percentage (5%) is in line with the national standard guidelines for economic evaluations. However, the specific discount percentage will be determined after conducting a sensitivity analysis, considering discount rates between 0% and 5%. Then, we include information from this analysis, explaining that the discount rate will be determined only after the analysis of the collected data. We modified the information and added references as follows: "sensitivity analysis will be performed with the costs data, considering 0% to 5% discount rate to define the optimal discount rate for the data, according to methodological Guidelines for Economic Evaluation of Health Technologies – Brazilian Ministry of Health."

Lines 381-2: The two techniques have different surgical costs (eg. arthroscopic set etc). These should be mentioned in detail in this section.
Answer: The information about the cost of arthroscopic surgery was added in the sentence:
"The costs included in direct medical costs will be: hospitalization, costs related to arthroscopic instruments (eg cannulas, shaver blades, suture passer, ablator) medical fees, medication; the indirect costs: costs of absence from work, which will be estimated by the patient-reported number of days away from work multiplied by the average wage rate of the current year."

Line 383: Change the word 'absenteeism' with 'absence' or 'loss of working hours' or something similar.
Answer: As suggested by reviewer the word "absenteeism" was change to "absence".

Line 410: Consider changing the word 'numerical' to 'continuous variables'
Answer: As suggested by reviewer the word "numerical" was change to "continuous variables".

Lines 419-420: Please add in brackets the company and the country of origin for SPSS, intended to be used.
Answer: The information of SPSS was included:
"(SPSS Inc., Chicago, Illinois, USA)"

Line 448: Consider changing the word 'reversed' with 'resolve'
Answer: As suggested by reviewer the word "reversed" was change to "resolve".

Discussion
Line 487: Try to avoid words as 'elegant' in the manuscript.
Answer: As suggested by reviewer the word "elegant" was change to "important".

Line 515: A typo mistake on VAS.
Answer: The writing of the acronym VAS was corrected

VERSION 2 – REVIEW

REVIEWER	Efthymios Iliopoulos Brighton & Sussex University Hospitals United Kingdom
REVIEW RETURNED	31-Oct-2020

GENERAL COMMENTS	Thank you for the opportunity to review the revised version of this manuscript. The authors have made some significant corrections in the manuscript, which has improved it considerably. All of the reviewers' comments have been addressed adequately. A few more minor comments: In the strengths & limitations section the third bullet point after the coma doesn't make sense. Please consider revising. Line 386: Consider revising the sentence to: 'If a patient becomes not reachable at any point of the follow-up,...'

VERSION 2 – AUTHOR RESPONSE

Reviewer requests:

In the strengths & limitations section the third bullet point after the coma doesn't make sense. Please consider revising.

Answer: The phrase was revised as follows: “This study will provide important information about rotator cuff healing and retear rates, what is still unclear in the literature”.

Line 386: Consider revising the sentence to: 'If a patient becomes not reachable at any point of the follow-up,...'
Answer: as suggested, the sentence was revised, as follows: “…he will be contacted by phone and e-mail. If a patient becomes not reachable at any time of the follow-up, we will consider a lost follow-up scenario…”