Author's response to reviews

Title: Clinical investigation for displaced proximal humerus fractures in the elderly. A randomized study of two surgical treatments: Reverse Total Prosthetic Replacement versus angular stable plate Philos (The DELPHI-trial).

Authors:

Tore Fjalestad (torfja@online.no)
Petter Iversen (peiverse@mac.com)
Margrethe Øye Hole (maohol@ous-hf.no)
Morten Smedsrud (mortensmedsrud@hotmail.com)
Jan Erik Madsen (j.e.madsen@medisin.uio.no)

Version: 7 Date: 3 May 2014

Author's response to reviews: see over

Fjalestad T. MD, PhD A
torfia@online.no Corresponding Author
Iversen P. MD A
torjofja@online.no
Hole MØ. PT B
peiverse@mac.com
Smadsrud M. MD C
maohol@ous-hf.no
Madsen JE. Professor, MD, PhD A
cmortensmedsrud@hotmail.com
j.e.madsen@medisin.uio.no

Thanks to the reviewers for their comments and corrections. Below there are point to point corrections or comments according to the reviewers specific questions. The corresponding corrections have been made in the new version of the study protocol, and appear in the text as **underlined in blue font**. Also new figures (4, 5 and Flow Chart) has been added.

Sincerely
Tore Fjalestad, first author.
On behalf of the authors

Version: 5
Date: 9 March 2014
Reviewer: Jinn Lin

1. The reliability of the consistency of the preoperative fracture classification should be described. It’s better to score the fracture severity, which can be used in stratification during patient recruitment. Besides, the experience and skills of the surgeons should also be controlled in this so technically dependent operation procedure.

Authors answer: A sentence has been inserted to focus the problem in the paragraph of Radiographic evaluation, as this issue already has been mentioned in line 339-340 and references 70-71. Concerning scoring of the radiographs, the degree of displacement reflects the severity. Stratification is based on gender and age, which is an important predictor without any risk of confounding. The skills of the attending surgeons are important, and has been emphasized in line 238-39 and in line 459 in version 5. A new sentence has been added in the chapter Surgical technique to specify this (page14).

2. How the adjusted Constant score is analyzed in the follow-up should be addressed.

Authors answer: The adjusted Constant score ACS will not be analyzed separate, as the CSD is the primary outcome to be used in analyzing functional outcome. The ACS is calculated from the CS of the injured shoulder. This has been corrected to emphasize that it is not a primary outcome. The way to calculate it has been addressed, and it has been moved to the last part of the chapter.
3. In the operation procedures of open reduction and internal fixation, deltopectoral approach is not the preferred surgical approach right now, compared with the anterolateral approach.

Authors answer: Our first priority was to avoid any bias between the two surgical treatments, using the same surgical approach. The supralateral or anterolateral approach is not fitted to control reconstruction of the important medial support by anatomic re-reduction and if necessary, by a 2.4 mm. additional plate as adjuvance in the ORIF-group (fig1). Also, splitting of the deltoid muscle may cause harm, and thus confound the results (Molé D., CORR 2011). This approach has not been proved superior for Reversed Prothesis or ORIF (Lädermann A., Orthop Traum Surg Res 2011, Buecking B. et al, CORR, 2013, Level 2 trial).

4. Concerning the surgical technique, how the intraoperative fluoroscope is used should be described. It has been widely reported that intraoperative bone grafting is beneficial for these comminuted proximal humeral fractures. This should also be considered.

Authors answer: I regret that I do not understand the reason to describe how to use intraoperative fluoroscope in any more detail. This is a standard procedure for every shoulder surgeon/ trauma surgeon to control reduction and screw positioning (implant position), as already described. Intra-operative bone grafting has been reported in different ways (autologous, bone substitutes, strut-grafts inside the bone e.g.), but this is level 4 evidence at present, and not widely used. To the authors’ experience, the mode of osteofixation is the most important. However, this has now been focused in the surgical procedure description and discussion (page 15 and page 19).

5. In method of randomization, the PI should explain how to stratify the patients, by age, gender, severity, et.?

Authors answer: This has been corrected.

6. In power analyses, how is Constant Score Difference used for sample size estimation. Similarly, how is it analyzed in the follow-ups?

Authors answer: The calculation of the power / sample size has been emphasized. The CSD will be calculated in the same way for all follow-ups.

7. The statistics is too rough. Obviously, this is a comparison of means or proportions with repeated measurements. It should be explained in detail.

Authors answer: This has been corrected and specified in this chapter.

8. How are the patients who are converted from ORIF to arthroplasty, if any, analyzed?

Authors answer: The intention to treat principle will be adopted; all patients will be analyzed according to their initial treatment groups. Crossovers will additionally be reported individually, This has been emphasized in Statistics.

9. The PIs do not mention the criteria for stopping guidelines. Meanwhile, the monitor or audit system should also be described.
Authors answer: This has been corrected within this chapter.

10. What are the definitions of the X-ray measurements in both groups? They should be clearly described with graphics. Figure B is missing. How can they be consistent among the observers? Besides, how is the X-ray position kept the same for each check up?

Authors answer: Figure of radiographic scoring for Philos plate and Avascular head necrosis has now been added (figure 4 and figure 5 in Appendix). The figure explaining the scoring of reverse prosthesis has been present (figure 3).
Two independent senior consultants with broad experience will examine all radiographs from all centers: This has now been described in the Method chapter page 11.
The staff at the radiographic department have been instructed on how to take standardized trauma projections before inclusion started. This was a part of the educational program given at all attending hospitals. It will be described in the final paper.

11. Other confounding factors, such as the comorbidities, degree of osteoporosis, trauma mechanism, etc. should also be recorded and analyzed. In the exclusion criteria, the definition of the alcohol- or drug abuse, dementia, neurological diseases, or severe 271 cardiovascular or lung diseases should be provided.

Authors answer: Data on co-morbidities and trauma mechanism will be collected, and presented in the final report. The precise degree of osteoporosis will need to be assessed with DEXA-scan, in addition to history of former fractures. DEXA-scan is not planned as a part of this study, as we have data on this issue for the same population and age / gender distribution. (Fjalestad et al. 2009. Proximal humeral fractures and relation to osteoporosis. A cohort study of 49 hospitalized patients with 50 fractures).
Precise definitions of alcohol- and drug abuse, dementia, neurological diseases, heart- and lung disease will be specified in the final report.

12. The rate of postoperative infection, which also needs a clear definition should be recorded?
Authors answer: A precise definitions of postoperative infection have been added in the text at page 18.

13. There should be a flow chart describing the timetable for all the postoperative assessments.
Authors answer: The Consort group standardized flow chart will be used to report every patient. This has been added as figure 6.

14. Group 1 and 2 in the Table 1 are reversed.

Author answer: This has been changed in a new table.

Version: 5
Date: 8 April 2014
Reviewer: Guido A Wanner

Reviewer's report:
Comments as minor revisions:

1a. According to the power calculation, the minimum number of patients to be included in the study is 51 patients/group, and the authors choose to include 60 patients/group. However, according to page 13 (‘Interventions’), only 55 patients in each group will undergo surgical treatment. This should be clarified.

Author answer: The number of patients needed is 51 in each group, however due to possible loss of patients, the number to be included will be 60 in each group. This has been corrected and emphasized.

1b. Likewise, there is a discrepancy regarding the time period of patient recruitment (until autumn 2015 [p. 17, line 550] vs. spring 2016 [p. 13, line 421]).

Author answer: This has been corrected: The last paragraph at page 17 was a duplicate that was planned to be removed, but forgotten. This has now been done.

1c. Another question is if the age of the patient cohort as well as the rather long follow-up of 5 years has been taken into account in order to prevent the study to be underpowered.

Author answer: This may be a problem. However, the plan is to publish at two year as “short term follow-up” (enough information for Philos according to literature, but not sufficient for prosthesis FU) and at five year as “medium term follow-up” due to the need of prosthesis replacement. Our experience with RCT and two year FU (e.g. ref. 16) for the same population of patients, with a mean age of approx. 72 years, is that 8-15% are lost to follow-up at two years (15% of 60 patients equals nine patients). If power should secure enough power at five year, the number needed to include will make it difficult to close enrollment within 3-3.5 years, and engaging more hospitals would be a logistic challenge. Therefore this has been compromised.

2. The statements regarding the length of follow-up are inconsistent: 2 years (p. 7, line 215), 5 years (p. 7, line 225, p. 13, line 402, and abstract), or even 10 years (p. 19, line 631). Please clarify.

Author answer: 2 and 5 years FU is correct. Line 215: and five years.. are added. Page 19: ...in addition to this protocol.. has been added, as this is not a part of the planned protocol, but some final thoughts.

3. When are radiographic evaluations performed during follow-up? After 12 and 24 months only (p. 11, line 351)?

Author answer: At every follow-up: New text: …at three and six months, thereafter at one, two and five years.

4. The number of participating surgeons (one surgeon per study center?) and their skill levels/experience with both treatment options should be specified.

Author answer: New text that emphasizes the way of reporting the surgeons experience and number of procedures according to the Consort statement has been written in the first part of the paragraph Operative technique (page 14) (Ref. 4)
5. How can the physiotherapists be blinded (semi-blind study design) if the time line of physical therapy for both groups substantially differs?

Author answer: The physiotherapist who perform follow-up examination at each center do not take any part in the treatment of the patients or their instructed physiotherapy. All physiotherapists have been trained at special workshops before inclusion started. They meet the patients the first time at 12 weeks and later on for examination, and at this time the timeline merges (table 1).

6. Is the surgical approach standardized for both groups (p18, line 581)? The statements on page 14 (lines 443 and 465) are somewhat misleading. With respect to the surgical technique, occasional use of a medial buttress plate and/or bone grafting in the control group (Philos) might affect the outcome. This should be discussed.

Authors answers: Standardized has been added to the text, as this is our approach for both groups (also mentioned in the fist part of the Discussion-part). The use of a medial 2.4 mm. buttress plate will also be reported for each case, and might be a bias as it intends to reduce failures of osteofixation. A new paragraph has been added to the Discussion part (page 18).

7. Although the study design can be regarded as state of the art, the question remains if it keeps its informative value by the time it will be published due to improvements/changes of implants (given the follow-up of 5 years). Another concern with these types of studies is if conditions can be identified, in which patients benefit from either treatment, and, thus, the study can provide help for decision-making in the individual patient situation. This should be also addressed in the Discussion section.

Authors answer: New designs of implants is a continuous process. To evaluate if they really represent improvements, RCT’s are needed. The number of different implant and prosthesis designs for proximal humeral fractures are numerous, although the amount of evidence at level 1-2 is very sparse. Therefore, both short- and medium time follow-up (at 2 and 5 years) is indicated. New text has been added to focus this in the last part of the first paragraph of the discussion, were this issue already has been addressed (page 19).
p 11, line 376 Would suggest “Arthroplasty” instead of “Artroplasty”.

Author answer: Corrected

p 11, line 355 What about the lateral displacement as a predictor for avascular head necrosis as described by Hertel et al (Ref 20). This usually would be a strong argument for arthroplasty in any patient and should be documented for a post-hoc confounding factor analysis.

Author answer: The lateral displacement corresponds to the medial hinge integrity or loss of this, as first described by Hertel in 2004 (ref. 20), later by Kralinger 2009 (ref. 51). Line 359, page 11 in version 5. Although Hertel has proved a high risk of ischemic humeral head with disruption of the medial hinge as one of four main predictors, an avascular head necrosis has not yet been proved to cause a poor outcome in elderly persons. Thus “a strong argument” still is a level 4 (5) evidence.

p 13, line 416 Inclusion “started”...?

Author answer: Corrected

p 13, line 427 In line 425 it says “60 patients” in line 427 and 429 it’s 55. Where did the others get lost?

Author answer: The number is 60 patients in each group. This has been corrected.

p 17, line 543 This paragraph is very similar to the paragraph on p 13, line 416 with the inclusion still starting in the past but now predicting end of inclusion in autumn 2015 (vs. spring 2016). Please delete one of both paragraphs and adapt time specifications.

Author answer: Line 543 – 550 has been removed. This double paragraph was meant to be removed before submitting the paper the first time. Corrected

5. Discussion

p 19, line 626: “have been reported” instead of “has been..”

p 19, line 627: “design” instead of “designs”

Author answer: Corrected