

**Handoll HH, Keding A, Corbacho B, et al.** Five-year follow-up results of the PROFHER trial comparing operative and non-operative treatment of adults with a displaced fracture of the proximal humerus. *Bone Joint J* 2017;99-B:383-392.

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**RE: answer to our previous letter (initial submission dated Nov. 27)**

19 December 2017

Sir,

Thank you for the opportunity to respond to the comments by Handoll et al in reply to our letter to the Editor.

We acknowledge that the PROFHER trial has several strengths. Notwithstanding, it also has some important limitations. These led us to conclude that the current PROFHER trial results should not be generalised to the majority of patients with displaced fractures of the surgical neck of the humerus. Our letter to the Editor referred to the most recent publication of PROFHER (five-year results) and the first report in *JAMA* in 2015. The issues we raise are not specific to an individual publication but to the trial itself.

Other publications have indeed provided further details (referenced by Handoll et al)<sup>1-5</sup> but they do not resolve all methodological issues raised in our letter, such as the generalisability of the findings, why most surgeons only operated on one to two trial patients each, and issues with the use of the Oxford Shoulder Score in patients with a fracture of the proximal humerus.<sup>6</sup>

We did not make any claims based on the subgroup analyses in the meta-analysis by Sabharwal et al<sup>7</sup> for the same reasons that Handoll et al have previously given. Our comment referred to the heterogeneity between studies, and that subgroup analyses suggest reasons for this.

Concerning the User's Guide to the Medical Literature,<sup>8</sup> the PROFHER trial was only used as an example to illustrate generic aspects to consider when interpreting surgical trial publications. The article did not address our specific comments.

Finally, Handoll et al should be aware that per-protocol analyses are indeed often used in clinical trials, such as non-inferiority studies and intention-to-treat analyses.<sup>9</sup> Given the conclusion of "no difference in outcomes" in the PROFHER trial, per-protocol analyses are expected because of the potential for non-compliers to bias the results in favour of no difference, particularly when they are clearly imbalanced between the trial arms.

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1. **Handoll HH, Keding A, Corbacho B, et al.** Five-year follow-up results of the PROFHER trial comparing operative and non-operative treatment of adults with a displaced fracture of the proximal humerus. *Bone Joint J* 2017;99-B:383-392.
2. **Handoll H, Brealey S, Rangan A, et al.** The ProFHER (PROximal Fracture of the Humerus: Evaluation by Randomisation) trial - a pragmatic multicentre randomised controlled trial evaluating the clinical effectiveness and cost-effectiveness of surgical compared with non-surgical treatment for proximal fracture of the humerus in adults. *Health Technol Assess* 2015;19:1-280.
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Conflict of interest statement: Simon Lambert, Martin Jaeger and Stefaan Nijs have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article, and benefits have been or will be directed to a research fund,

foundation, educational institution, or other non-profit organisation with which one or more of the authors are associated.

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