PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Platelet Rich plasma Injection Management for Ankle osteoarthritis study (PRIMA) Protocol of a Dutch multi-center, stratified, block-randomized, double-blind, placebo-controlled trial
AUTHORS	Paget, Liam David Andrew; Bierma-Zeinstra, Sita M.A.; Goedegebuure, S; Kerkhoffs, Gino M.M.J.; Krips, R; Maas, Mario; Moen, Maarten H; Reurink, G; Stufkens, Sjoerd A.S.: de Vos, Robert-Jan; Weir, A; Tol, J L

VERSION 1 – REVIEW

REVIEWER	Jun Liu The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.
REVIEW RETURNED	11-Jun-2019

GENERAL COMMENTS	The protocol is well designed. This paper has a potential to be accepted. Can you discuss the mechanisms for PRP injections in the treatment of ankle OA? In addition, is there a statistical expert involved in your clinical trial?

VERSION 1 – AUTHOR RESPONSE

Reviewer: The protocol is well designed. This paper has a potential to be accepted.
Response to reviewer: We thank the reviewer for his/her kind words.
Action taken: None required

Reviewer: Can you discuss the mechanisms for PRP injections in the treatment of ankle OA?
Response to reviewer: We thank the reviewer for this point and have added a paragraph discussing the mechanisms of PRP.
Action taken: page 5 line 100-109:
“Platelet Rich Plasma (PRP) is defined as plasma containing a concentration of at least 1,000,000 platelets/µl.4 Growth factors are stored in α-granules within platelets, and are released in a selective manner upon activation. Growth factors released from the α-granules of platelets are assumed to provide the regenerative benefits of PRP.
Recent reviews concluded that in animal models PRP can diminish multiple inflammatory IL-1 mediated effects.5 Due to this local anti-inflammatory response, PRP might have an indirect analgesic effect. The second suggested effect might be protection of the cartilage from destructive pro-inflammatory interleukines. This is mediated due to an increased mRNA expression of proteoglycan core protein in the articular cartilage and decreased chondrocyte apoptosis.5 Consequently, PRP could positively influence the collagen network of the cartilage.”

Reviewer: In addition, is there a statistical expert involved in your clinical trial?

Response to reviewer: We do indeed have a statistical expert and have added this to the protocol accordingly.
Action taken: page 18, line 364: “A statistical expert (SB) is present among the authors.”