

## Reviewer's comments and responses

10<sup>th</sup> September 2014



Dear Editor,

Please find enclosed the edited manuscript in Microsoft Word format (file name: **12240-review-edited2.doc**) and also a manuscript depicting all our track changes (file name: *12240-review-edited with all track changes.doc*)

**Title:** Oral creatine supplementation; a potential adjunct therapy for rheumatoid arthritis patients

**Author:** Wilkinson, Thomas James; O'Brien, Thomas Daniel; Lemmey, Andrew Bruce

**Name of Journal:** World Journal of Rheumatology

**ESPS Manuscript NO:** 12240

We thank all the referees for their judgments and comments, and appreciate that they found our review "Oral creatine supplementation; a potential adjunct therapy for rheumatoid arthritis patients" to be both "good" and "interesting". In accordance with the comments from the reviewers, here are the amendments and our clarifications:

### **1) Reviewer 00505365:**

In agreement with the wishes of this reviewer we have shortened the review, particularly the 'Introduction'. Although we have reduced this part, we have not removed much content from the *Mechanisms* section as we feel this provides important context and information that helps the reader understand how and why creatine may be effective in increasing muscle mass and improving function in RA.

In response to other comments made by this referee:

*"Alterations in physical functions, lean mass and strength in RA depend on many factors such as arthritis, arthralgias, contractures and types of the (sic) medical therapy agents etc".*

We readily acknowledge this point, and have not stated otherwise in our review. Although there are indeed many mechanisms contributing to the impaired physical function and body composition in RA, there remains a need for general, widely-applicable adjunct therapies for this population. This is especially true since despite the profound improvements in pharmacological treatment, loss of muscle mass and increased adiposity, and (largely as a consequence of these adverse changes in body

composition) impaired physical function, remain characteristics of RA. In fact, an on-going study being performed by our group shows that the current “Treat-to-target” therapy is having little or no effect in improving either body composition or objectively assessed physical function (which remains about 20-30% poorer than that of age- and sex-matched sedentary controls). This is explained in detail in the review, as is the inability of anti-TNF agents to improve body composition (which was initially demonstrated by our group). In contrast, as also clarified in our review, high-intensity exercise can restore both body composition and objectively assessed function (e.g. studies from our group: Lemmey et al, 2009; Marcora et al, 2005), but this adjunct treatment option is rarely performed regularly by patients. So clearly there is a need for a widely acceptable adjunct therapy for improving body composition and physical function in RA and, for the various reasons described in the review, oral creatine supplementation is an obvious candidate for this.

*Comparison with OA, fibromyalgia, muscular dystrophy etc:*

We are not suggesting that the pathologies of these conditions share commonality with RA; but they do share some of the same symptoms as RA (e.g. muscle loss, impaired function, fatigue, and bone loss). Therefore looking at how creatine supplementation affects these symptoms in these other conditions is an obvious and logical course of action when evaluating the likely effects of supplementation in RA.

## **2) Reviewer 00227340:**

We thank this reviewer for their comments, and in accordance with their suggestions have made the following changes:

*“English language must be checked”*

We checked the manuscript for spelling and grammatical errors, as well as for conciseness and reading flow.

*“References are not in accordance with authors guidelines”,*

The references were checked again for order and formatting. All full journal titles in the reference list were changed to the abbreviated format in line with the author’s guidelines (eg, *J Clin Nutr*). As suggested all references were checked on CrossRef.org using the Simple Text Query Form Version 1.4.5, this meant that all titles with available information such as DOI and/or PMID were updated.

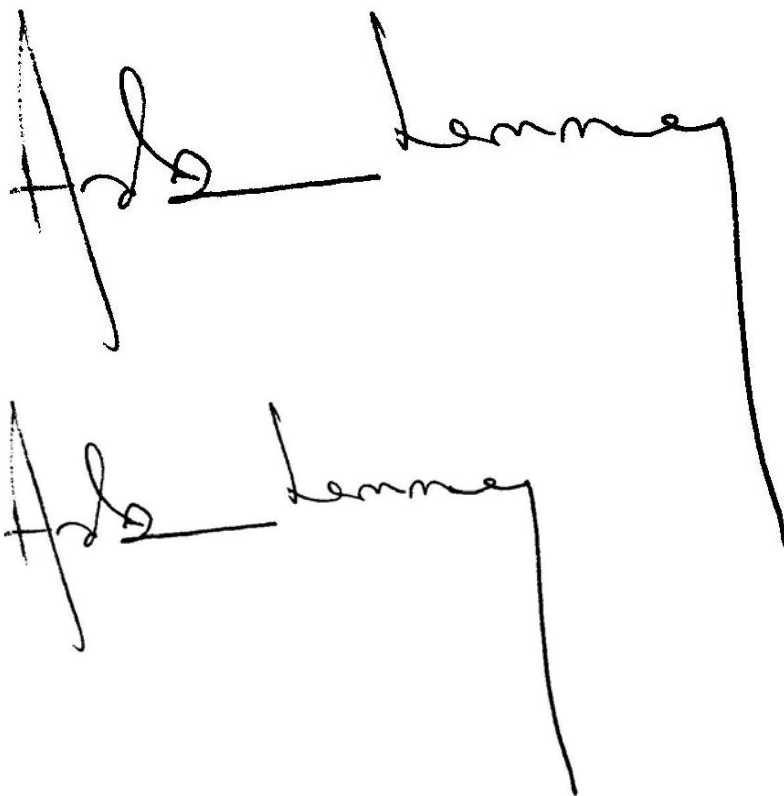
*“Quality of tables should be optimized”*

In regard to this comment, the tables were checked for formatting errors in line with the

journal guidelines. The *n* denoting number of participants was changed to italics, the *P* donating probability was capitalized and italicized (*P*), and the value for  $P < 0.05$  was amended to fit in with the authors formatting guidelines (<sup>a</sup>*P* < 0.05). Several border lines that were out of place were removed.

### 3) *Suggested changes on manuscript from editor:*

As suggested by comments on the manuscript, the full names are now given for each author as well as postcodes for addresses in Bangor and Liverpool. There is additional road/street information on the 'Correspondence address, and as requested in the tables, the abbreviation 'vs' has been described in the table legend (vs: versus).

A handwritten signature in black ink, appearing to read 'A. B. Lemmey'. The signature is written in a cursive style with a long horizontal line extending to the right.

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