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)	Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis: protocol for a prospective, exploratory cohort study.
AUTHORS	Højgaard, Pil; Christensen, Robin; Dreyer, Lene; Mease, Philip; Wit, Maarten; Skov, Lone; Glintborg, Bente; Christensen, Anton; Ballegaard, Christine; Bliddal, Henning; Bukhave, Kirstine; Bartels, Else; Amris, Kirstine; Ellegaard, Karen; Kristensen, Lars Erik

VERSION 1 - REVIEW

REVIEWER	Vinod Chandran University of Toronto and University Health Network, Toronto, Canada
REVIEW RETURNED	12-Dec-2015

GENERAL COMMENTS	The authors propose to conduct an important study that will inform clinical practice. My suggestions/comments are: 1. My primary concern is that the composite outcome measures proposed have been developed for RA and not for PsA. I agree that these measures have performed well in polyarticular PsA in clinical trials. This study is however being conducted in routine care and thus these measures may not be appropriate. Why are composite outcome measures such as PASDAS, GRACE index or CPDAI not being considered? 2. Participants; line 4- It is better to state that the patients will be diagnosed by a rheumatologist and classified according to the CASPAR criteria. 3. Participants; line 7- I am concerned that since some patients may have a rapid response to treatment assessment within 15 days of treatment initiation may be problematic. 4. Clinical examination; line 3- The SPARCC enthesitis index evaluates 18 sites, with a maximum possible score of 16. 5. Page 11, line 25- The MDA criteria does not include BASDAI. 6. SF-36- Are the authors evaluating the PCS or MCS or both?

REVIEWER	Burkhard F. Leeb 2nd Dept. of Medicine Center for Rheumatology Lower Austria
REVIEW RETURNED	06-Jan-2016

GENERAL COMMENTS	The main concern is the enormous amount on outcome measures to be applied. I wonder if the participants will be able to follow all the questionnaires and procedures. One may have the expression that the amount of measures shall allow the answers one wants to get or this protocol was created by theoretical rheumatologists not

	considering how long a patient will have to stay in the out-patients clinic to complete all the stuy related procedures. By the way could the authors please give the validation paper for the ACR criteria in PsA and the PsAID. And, why intend the authors to apply RA-disease activity indexes, although they have been never validated in PsA. Their frequent application does not necessrailiy make them formally validated and thereby justified to be applied in PsA.

REVIEWER	MIRIAM TEOLI UNIVERSITY OF ROME TOR VERGATA ITALY
REVIEW RETURNED	15-Jan-2016

GENERAL COMMENTS	PAGE 12, LINE 13 WORD: CRITERION CHANGE INTO CRITERIA

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
1. My primary concern is that the composite outcome measures proposed have been developed for RA and not for PsA. I agree that these measures have performed well in polyarticular PsA in clinical trials. This study is however being conducted in routine care and thus these measures may not be appropriate. Why are composite outcome measures such as PASDAS, GRACE index or CPDAI not being considered.

Our reply: Thank you for this important comment, we certainly agree with your point of view. We chose DAS28 and ACR criteria as outcome measures due to their familiarity among clinicians and their widespread use in clinical PsA trials, as well as in routine care. Being aware of the shortcomings of these measurements for PsA, we included Minimal Disease Activity (MDA) and change in certain domains as PsA-specific outcomes. However, we agree that the development and validation of composite outcome measures for PsA should be valued, and therefore we have added the PASDAS as an additional outcome as you suggest. The PASDAS covers physician and patient global VAS assessment, the physical component score (PCS) of the Medical Outcomes Survey-Short Form-36 (SF-36), a 66/68 joints count, enthesitis (Leeds Enthesitis Index, LEI) and dactylitis (count), as well as CRP. The current examination program contains all these component of PASDAS except for one detail: The SPARCC does not assess the “medial femur condyl” (MFC) enthesis. To overcome this problem (as participants are already being included) we will perform a slight modification by substituting the MFC (part of LEI) with the enthesial site at the proximal patella (part of SPARCC), and refer to the outcome as mPASDAS. Both the change in PASDAS, as well as achievement of PASDAS good response, will be evaluated. Please see the red changes in text (p.9) and table 3.

2. Participants; line 4- It is better to state that the patients will be diagnosed by a rheumatologist and classified according to the CASPAR criteria.

Our reply: That is an important notion, thank you. We have revised as suggested.

3. Participants; line 7- I am concerned that since some patients may have a rapid response to treatment assessment within 15 days of treatment initiation may be problematic.

Our reply: Thank you for this extremely useful comment. We make every effort to include participants at an early time point. Based on the inclusion so far (20 participants), we do find it possible to narrow down the baseline interval, so that participants will be examined from 15 days before intensification of

medicine to 7 days. This will reduce the “risk” of a rapid response. The change has been inserted in the section: METHODS; “Study Design” (p.3).

4. Clinical examination; line 3- The SPARCC enthesitis index evaluates 18 sites, with a maximum possible score of 16.

Our reply: Thank you for this correction. We have adjusted accordingly.

5. Page 11, line 25- The MDA criteria does not include BASDAI

Our reply: Thank you for making us aware of this mistake, which has now been corrected.

6. SF-36- Are the authors evaluating the PCS or MCS or both?

Our reply: Thank you for asking clarification for this. We are evaluating both PCS and MCS and have now specified this in the protocol. (Red changes in: table 1, table 3, text p.7-8)

Reviewer 2:
1. The main concern is the enormous amount on outcome measures to be applied. I wonder if the participants will be able to follow all the questionnaires and procedures. One may have the expression that the amount of measures shall allow the answers one wants to get or this protocol was created by theoretical rheumatologists not considering how long a patient will have to stay in the out-patients clinic to complete all the stuy related procedures.

Our reply: Thank you very much for this important consideration. We agree that feasibility is a very important issue and that the program might look overwhelming at first sight. However, the Parker Institute possesses all necessary facilities, clinical staff, experience and routine to plan and perform clinical studies. To date, 20 participants have completed the baseline program (3-4 hours). Our impression is that the participants appreciate the thorough examination and interview - and everyone has completed all questionnaires.
We understand your concerns regarding the multiple outcomes. The study design allows an explanatory investigation of pain mechanisms, US pathology – and the association and prognostic impact of these measurements - in the absence of a pre-specified hypothesis/primary outcome. We found this strategy appropriate given the heterogeneity of PsA and the sparse knowledge/lack of gold standards currently available within this research field. We realize that this exploratory approach may limit the strength of our conclusions, and have added these considerations to the "discussion" section and to the section of "strengths and limitations".

By the way could the authors please give the validation paper for the ACR criteria in PsA and the PsAID. And, why intend the authors to apply RA-disease activity indexes, although they have been never validated in PsA. Their frequent application does not necessrailiy make them formally validated and thereby justified to be applied in PsA.

Our reply: Thank you for addressing these important issues. We are aware that ACR criteria are not validated in PsA. We agree that the wide use of ACR20 as a primary endpoint in clinical PsA trials do not justify the extrapolation from RA to PsA. However, ACR20 (and DAS28) are response criteria that most clinicians/readers are very familiar with and can easily interpret. Besides, these outcome measures have shown acceptable discriminative capacity in clinical trials of PsA polyarthritis.(Ann Rheum Dis 2006 Oct;65(10):1373-8. Epub 2006 Apr 27. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Fransen J, Antoni C, Mease PJ et al).
Based on these considerations we prefer to keep ACR20 (and DAS28) as outcomes as explained in

the section: "exploratory outcomes and response criteria", (p.10) where the reference above is now added. However, we agree with you (and reviewer 1) that PsA specific measures are of primary interest and have also included PASDAS as an outcome (in a slightly modified version). Please see our reply (1) to the first reviewer for further details/explanation on this, thank you.

Regarding PsAID: Thank you for a very important remark: We agree that the PsAID has only been pre-validated. We have adjusted the phrasing (pre-validated instead of validated) in the section "Patient demographics and patient-reported outcomes" and apologize for this mistake. (Red changes in text p. 7)
Ann Rheum Dis. 2014 Jun;73(6): A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. Gossec L, de Wit M, Kiltz U, Braun J et al; EULAR PsAID Taskforce.

Reviewer 3:
1) PAGE 12, LINE 13 WORD: CRITERION CHANGE INTO CRITERIA
Our reply: Thank you for this correction. We have changed MDA criterion to MDA criteria throughout the document.

VERSION 2 – REVIEW

REVIEWER	Vinod Chandran University of Toronto, Canada
REVIEW RETURNED	17-Feb-2016

GENERAL COMMENTS	Thank you for revising the manuscript appropriately. My only suggestion is to include collection of data on narcotic analgesics at follow up. I understand that patients on narcotic analgesics at baseline are excluded.

REVIEWER	Burkhard F. Leeb LANDESKLINIKUM KORNEUBURG-STOCKERAU LK Stockerau II. Med. Abteilung, NÖ Kompetenzzentrum für Rheumatologie; 2000 Stockerau, Landstraße 18
REVIEW RETURNED	26-Feb-2016

GENERAL COMMENTS	The authors could not resolve all doubts about the use of non-validated disease activity assessment tools in PsA patients, which were reaised by both reviewers. Another publication utilizing those instruments would only strengthen the situation to be under a misapprehension when applying those tools in PsA. Rheumatology in general has to commence to increase its overall transparency and its statistical as well as its analytical correctness.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Vinod Chandran
Institution and Country: University of Toronto, Canada Competing Interests: None declared
Thank you for revising the manuscript appropriately.

My only suggestion is to include collection of data on narcotic analgesics at follow up. I understand that patients on narcotic analgesics at baseline are excluded.

- Dear Reviewer 1,
Thank you very much for this important comment. It is a clear mistake that information on narcotic drugs doesn't appear in the protocol. The use of opioids, anti-depressants and anti-convulsants during the study will be registered at the 4 months follow up. We have now specified this in Table 1.

Reviewer: 2
Reviewer Name: Burkhard F Leeb
Institution and Country: LANDESKLINIKUM KORNEUBURG-STOCKERAU, Universität Wien, Austria
Competing Interests: None declared
The authors could not resolve all doubts about the use of non-validated disease activity assessment tools in PsA patients, which were reaised by both reviewers. Another publication utilizing those instruments would only strengthen the situation to be under a misapprehension when applying those tools in PsA. Rheumatology in general has to commence to increase its overall transparency and its statistical as well as its analytical correctness.

-Dear Reviewer 2,
Thank you for this important consideration. We fully agree that the validation of PsA outcome measurement instruments is needed and that we include some outcome measures which may not be appropriate for PsA. We know that OMERACT and GRAPPA is working to improve the selection of core domains and endorse appropriate instruments to assess these and hopefully more clarification will occur within few years.
In the current study we have highlighted the limitations of the instruments used in the "strength and limitation" section and in the discussion. We became aware that DAPSA could be an appropriate instrument to include, since it has been validated to at least some extent in PsA and cut-off values and response criteria have been provided. This outcome measurement is added to Table 2 and described (with appropriate references) in the Section "Exploratory outcomes and response criteria" (p.15).