Author's response to reviews

Title: Effectiveness of a Cognitive-Behavioral Group Intervention for Knee Osteoarthritis Pain: Protocol of a Randomized Controlled Trial

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AUTHORS' REPLY TO THE REFEREES

First of all, we would like to thank the referees for their valuable comments and criticism, which clearly improved our manuscript.

Referee 3:

Referee Comment:
“Page 3: To be correct, the Riddle et al study is not an RCT but rather a quasi-experimental design. Also, the Somers study is independent and separate from the Riddle study. This should be clarified in the paper.

Author’s reply:
We have made the suggested corrections and clarifications regarding the studies conducted by Riddle et al and by Somers et al. Please see the revised Background p. 5, 2nd paragraph.

Referee Comment:
Also there have been several trials of pain coping skills training (see Hurley et al and Keefe et al for examples) and other behavioral interventions that have been very similar to CBT with fairly extensive overlap with CBT based principles. These types of trials should be mentioned so as not to imply that the studies you mentioned are the only trials of CBT based interventions on persons with knee OA.”

Authors’ reply:
Indeed, while drafting the manuscript we found it rather difficult to decide which studies to include in the introduction because there are numerous studies with behavioural interventions similar to CBT and also interventions combining CB principles to other forms of rehabilitation. Now, we decided to write a separate chapter in the introduction to cover this group of studies. Please see the revised Background p. 5, 3rd paragraph – p.6 1st paragraph.

Referee Comment:
“Page 4: Please state the number of patients in each block. This is important for replication and for knowing whether study staff may be biased in estimating group assignment.”

Authors’ reply:
Randomization will be conducted in blocks of six, separately for men and women. We have now added the number of patients in each block to the manuscript, please see Participants and recruitment on p. 8, 3rd paragraph.

Referee Comment:
“Page 5: Please specify the roles of the physios versus the psychologists in care delivery. It is not clear what these clinicians will do and not do during the intervention. Also, please provide some description of the extent of training and how you will determine whether the clinicians are adequately trained to deliver the intervention and how you will determine whether the intervention was delivered as planned.”
Authors’ reply:
We have now specified the roles of the psychologist and the physiotherapist in delivering the CB intervention as well as described the training they have received for delivering the CB intervention in the text. Please, see revised Intervention on p. 9, 1st paragraph.

Referee Comment:
I also found not description of the contents of the intervention. A more elaborate description of the treatment elements along with who is responsible for each element would be helpful here. Perhaps a table summarizing these elements and their contents would assist the reader.”

Authors’ reply:
In the original manuscript the CB intervention has been described in Table 2 where an outline of each session in terms of its focus and the skills trained there is presented. In order to give a more elaborate description of the intervention program we added objectives of each session to Table 2. Please see revised Table 2 (pages 25-26). The timetable and the structure of each session has been described in the revised Intervention, Please see Intervention page 9, 1st paragraph. For those who are interested the contents of the CB intervention can be found in full detail from in the Session manual for therapists (Linton 2005).

Referee Comment:
“Obtaining and assessing KL grades are not as simple as they appear. Valid measures are dependent on knee flexed standing views and examiner experience. Please discuss how you will assure that the radiographic data will be valid.”

Author’s reply:
We fully agree that the obtaining and assessing KL grade are not a simple task. Valid measures are dependent on knee flexed standing views (Sun et al. 1997, Gunther and Sun 1999). and examiner experience (Sun et al. 1997, Gunther and Sun 1999). Although it has recognized weaknesses, the KL score has been the most widely used radiographic score to assess knee OA (Sun et al. 1997). We decided to use KL grade ≥2, which has been extensively used as the inclusion criterion in knee OA studies (Schiphof et al. 2008). Unfortunately, we will not be able to control the radiographic quality since the knee X-rays will have been taken in public primary care locations and in the outpatient clinics. However, we use the combined radiographic and clinical criteria that have been proposed for use when diagnosing knee OA. If one combines the clinical and radiographic factors, the sensitivity and specificity of knee OA diagnosis are 91% and 86%, respectively (Altman et. al 1986). The observers also will be well trained and acquainted with the radiographic atlas of the KL scores before the start any assessments. Although reliability for the separate KL radiographic features may depend on the level of the investigator’s experience, the intra- and inter-observer reliability for the overall score is known to be relatively high (Gunther and Sun 1999). We added a new chapter concerning the discussion of the validity of our radiographic data, please see revised Discussion on p. 14, 1st paragraph.

Referee Comment:
“Your exclusion criteria require some elaboration. For example, how will you screen for “Severe psychiatric or psychological disorder.” How will you determine if “Other back or lower limb pain symptoms are more aggravating than knee pain.” These judgements require data and in order for
your study to be replicable, you need to define methods for determining these criteria. Also, how will you determine if a potential subject is “unlikely to be compliant.” This also is important for replication and is relevant given you appear to be conducting a pragmatic trial.”

Authors’ reply:
The referee’s comment is valid. In the recruitment process potential patients will fulfil a preliminary questionnaire containing a comprehensive list of their comorbidities, including psychiatric illnesses. A psychiatric or psychological disorder was determined severe if psychotic illnesses or psychological disorders that had led to hospitalization or disability to work. Please, see the revised Table 1 and the participants and recruitment on p. 8, 2nd paragraph.

In the preliminary questionnaire the patients were also asked if they have other back or lower limb pain symptoms that are more aggravating than their knee pain (yes/no). If the patient had answered positively to this question he/she was excluded. Please, see the revised Table 1 and the participants and recruitment on p. 8, 2nd paragraph.

In recruitment a potential subject was determined “unlikely to be compliant” if there was, uncertainty about the strength or motivation to participate in the study due to yet undetermined plans or uncertain changes in the near future related to health or family and/or living conditions Please, see the revised Table 1.

Referee Comment:
“Evidence supporting the psychometric properties of the instruments on Finnish patients should be provided.”

Authors’ reply:
BDI-21, BAI, 13-item SOC scale, TSK, PSEQ and LS questionnaires have been used in several clinical studies in Finland [see the revised manuscript references: 37, 38, 40, 45, 46, 50, 52-55, 68, 69]. However, at present BDI-21 and 13-item SOC scales have been validated in Finland [see the revised manuscript references: 68, 69] and the validation process of TSK is almost complete. We have available translated versions of separate questionnaires that have been in use in clinical studies and clinical routine in Finland. As the psychometric questionnaires are all secondary outcome measures in our study we decided to include them even though there is a shortage of supporting evidence for the validity of some of their psychometric measurement properties in Finnish patients. We added a new chapter concerning the discussion of the psychometric properties of the instruments on Finnish patients, please see revised Discussion on p. 13, 3rd paragraph and see the revised Table 3.

Referee Comment:
“The attention given to the two groups is different. Patients assigned to the CBT group will receive 12 more hours of attention relative to the control group. How will the authors determine whether any effects found are due to attentional effects versus actual improvement due to CBT?”

Authors’ reply:
This is a very good comment. One limitation of the study might be the different amount of attention paid to the two groups. As the group of patients in the intervention will receive 12 hours more attention, a Hawthorne effect [see the revised manuscript references: 65-67] is probable. However, all patients will receive the same basic instructions about knee OA treatment according to Finnish
CC guidelines when they are listening to a lecture delivered by a general practitioner prior to the randomization. This lecture will be held in groups of about 20 people and the whole research group will be present to answer questions. During the lecture the patient-version booklet of Finnish CC guidelines on hip and knee OA will be handed out to all participants. The participants in both groups also will continue to receive standard care (i.e. normal routine care offered by their own general practitioners including analgesics and physiotherapy). We added a new chapter concerning the discussion of the group attention and Hawthorne effect, please see revised Discussion on p. 13, 2nd paragraph.

**Referee Comment:**

"The power analysis does not provide a description of the effect expected and thembases for this effect. It is also unclear why you chose to use WOMAC scores different from the Tubach paper. Please clarify."

**Authors’ reply:**

The mean (±SD) knee joint pain score (WOMAC (VAS)) was estimated by using the results of the knee joint pain scores in the previous studies (Tubach et al. 2005 and Liikavainio et al. 2008). In the study by Tubach and co-workers patients (n=603) had to experience pain from knee OA (>30 mm on a VAS varying from 0 to 100) and require treatment with a non-steroidal anti-inflammatory drugs (NSAID). In their study the mean VAS knee joint pain was 59.3±16.2 mm. In our study the requirement for the treatment with NSAIDs is not included and based on our previous cross-sectional study with knee OA patients (n=54) (Liikavainio et al. 2008) the mean WOMAC pain score was lower (KL2;29.8±25.1 mm, KL3;23.8±15.2 mm, KL4;40.8±15.4 mm). However, because the knee pain had to be ≥ 40 mm on a 100-mm visual analogue scale (VAS (WOMAC)) in our present study, we postulated a mean of at least 48±16.2 mm in the WOMAC pain subscale at baseline. In our study the 20% reduction in primary outcome (WOMAC pain) due to the intervention was considered as being clinically relevant in accordance with the OMERACT-OARSI set of responder criteria (Pham et al. 2004). To compare the mean pain scores between the groups, 54 patients per group are needed according to power calculation with the two-tailed Student t-test with a 5% significance level and 80% power, assuming a 20% dropout rate (Campbell et al. 1995). Please see the revised Statistical analysis on page 10, 4th paragraph.

**Referee Comment:**

“**There is no mention in the analysis section for how the cost utility analysis will be handled. No mention is made for how missing data will be handled. How will all the secondary measures be analyzed?**”

**Authors’ reply:**

Cost-effectiveness of the intervention will be evaluated by cost-utility analysis that incorporates the expenses of the intervention as well as the costs of the use of health care services and medication, sick leaves, rehabilitation and pensions. The use of health care and rehabilitation services and the use of pain medication, sick leaves and pensions are evaluated from the information gathered from the patients in the questionnaires. Utility analysis is based on measurement of QALY from 15D (Räsänen et al. 2007). Life expectancy with 0 %, 3 % and 5% discounting will be incorporated in the analysis. Cost-effectiveness of the intervention is evaluated by dividing the overall costs with the QALY. The measurements needed for the analysis are done at all follow-up points but our primary interest is at 12 months.
Randomly missing data in the longitudinal set-up will be imputed using last observation carried forward principle before the analysis in order to follow intention to treat principle.

All secondary measures will be analyzed at baseline, 3 and 12 months apart from global assessment of change that is asked only at 3 and 12 months. The primary end-point for all analyses is at 12 months. Data on various psychological variables predicting reported knee pain will be assessed by multiple regression analysis. For outcomes measured on a continuous scale, differences between groups in the mean change from the baseline to 12 months will be evaluated using linear mixed modeling. The model assumptions will be checked by standard diagnostic plots.

Please, see revised Statistical analysis on p. 11, 2nd – 3rd paragraphs.

Referee 2:

Referee Comment:
“However, in the abstract please provide a little more info on the blinding of the personnel within the study and list the secondary outcome measures.”

Authors’ reply:
We have added the sentence “Personnel responsible of the data analysis will be blinded.” Unfortunately, due to the limitations set by the word count we are not able to list the secondary outcome measure in detail in the Abstract. Please, see revised Abstract on p. 2.

Referee Comment:
“Please discuss the implications for cost of therapy as alluded to in the intro?”

Authors’ reply:
We have revised the first paragraph of the Discussion to include the implications of the cost of the therapy. Please, see revised Discussion on p. 12, 2nd paragraph. We have also added more information about how the cost-effectiveness and cost-utility analysis will be conducted in Statistical analysis. Please, see revised Statistical analysis on p. 11, 3rd paragraph.