Author’s response to reviews

Title: Effectiveness and Cost-effectiveness of Transmural Collaborative care with Consultation Letter (TCCCL) and Duloxetine for major depressive disorder (MDD) and (sub)chronic pain in collaboration with primary care: a randomized placebo-controlled Multi-Centre trial. TCC: PAIN Dip.

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Author’s response to reviews: see over
Cover letter revision article:

**Effectiveness and cost-effectiveness of transmural collaborative care with consultation letter (TCCCL) and duloxetine for major depressive disorder (MDD) and (sub)chronic pain in collaboration with primary care: a randomized placebo-controlled multi-Centre trial. TCC:PAINDIP.**

February, 2013

Dear Editor,

We thank the reviewers for their thorough reading and useful comments. We adjusted the article accordingly and believe the adjustments improved our article. In this cover letter we will address all the suggestions of the reviewers.

We hope for a quick response, since there already has been much delay since the first submission of this article. If you do have any questions, please do not hesitate to contact me.

On behalf of the research group, yours sincerely,

Eric de Heer
Reviewer 1:

- The references need updating – balance 2009 and earlier.
  - References have been updated and balanced (reference 8, 9, 10, 11, 14, 18, 21, 23, 27, 31, 33, 37, 48, 65, 66, 67, 71, 72, 86, 87 have been added)

- Consider Managing ...barkin, also see Bradley.
  - These references have been added (33 and 52)

The abstract:

- Change ‘burden’ to ‘comorbidity’. (page 2)
  - This has been changed and the sentence has been adapted accordingly

- Recognition is evolving, not low (page 2)
  - Added that recognition is evolving

- Predict a slower response as opposed to poorer (page 2)
  - The work of Huijbregts et al shows that the response to treatment is actually poorer, not slower

-tx of chronic pain in depressed pty is continuous as opposed to limited (page 2)
  - Research attention to this treatment has so far been limited, this is what we mean here and we adapted the sentence

- Integrated tx may not be financially provided by a payor/insurance.
  - We agree but that is not the topic of research here.

- During the 12 weeks what of physical pathology which responds to invasive interventions by anesthesiology/pm and r as lesi, blocks, dcs, implant pumps
  - To this attention is given if necessary. The psychiatrist can evaluate the additional need of physical interventions (e.g. through dossier inspection)

Background:

- '...chronic pain now have a risk of not receiving optimal care. (page 3)
  - 'the best possible care' has been changed to 'optimal care'.

- Define active monitoring (page 5)
  - Definition has been added

- Define cope (page 5)
  - Examples of chapters in the self-help manual are mentioned to give a clearer picture on possibilities of coping with complaints

- Elaborate on NMDA, glutamate, sub p, etc role in pain processing. (page 6)
  - We added several refs on that at page 6
- Elaborate on ascending and descending pathways with respective neurotransmitters for transduction, transmission, conduction, perception, etc. (page 6)
  - Information has been added on ascending and descending pathways for pain. References 50, 51, 52, 66 and 67 have been added to support this
- Study references should discriminate animal from human
  - References now discriminate between animal and human studies
- Reconsider the time for which pain is considered chronic, as acute pain resolves with wound resolution in about less than 15 days (page 7)
  Chronicity may be a function of a chronic underlying pathology or appear within 4-6 weeks of the initial trauma. (page 8)
  - Added nuance to the definition of subchronic and chronic pain, (page 7 and page 12)

Methods:
- Define units in the study etoh (page 11)
  - Unit has been defined
- Define drug abuse in the study (page 11)
  - Current use of hard drugs or cannabis is in this study enough to be excluded. Is already defined in the text
- Define clcr for renal dysfunction (page 11)
  - We did not use clearance as definition for renal dysfunction but excluded everybody under treatment for renal dysfunction. Renal dysfunction in history is checked, and if present and treatment is needed, the patient is excluded. Creatinine levels are not measured
- Define hepatic dysfunction without child pugh info and use lab indices (page 11)
  - We did not use lab indices as criterion for hepatic dysfunction but excluded everybody under treatment for hepatic dysfunction;
- Define hard drugs in the study (note states in the USA are legalizing deltas THC) (page 11)
  - Hard drugs are defined by Dutch law. This has been added to the text, as well as some examples of hard drugs. THC is already allowed in the Netherlands but THC use nevertheless was an exclusion criterium
- Which clinical urine drug testing did you employ in the study as presumptive or confirmatory
  In case of suspicion during clinical interview, urine testing is applied; we added this
- The word sorts...most patients present with both evidence of nociceptive and neuropathic complaints. (page 12)
  - Changed 'or' in 'and/or' and added a sentence which explains that our pain medication protocol can be used when both forms of pain occur at the same time in a patient
- Change opiates to opioids (page 13)
  - Has been changed
- Consultation Letter: How was 6 months established, and why 6 weeks and not monthly. What of chronic patients needing the augmentation of polymodal therapy with AED, opioids, SMR etc/lie
  - The Consultation Letter is used as an advice for the general practitioner. This advise is specifically designed for the complaints which the patient still has at the end of treatment (and is thus directed at depressive symptoms, pain complaints and medication for these complaints). The general practitioner can take upon himself to start treatment for other complaints. In this letter, we advice to continue medication for a period of 6 months, because that is the standard period as is advised in the 'NHG standard - depression', a guideline for general practitioners (reference has been added). 6 weeks monitoring was done as most medication needs 6 weeks before improvement can be assessed.

- List the specific number of patients specific dx as plps, dpn, lbp, limb pain, joint pain, cervical, thoracic, lumbar, sacral, spinal stenosis etc
  - This information is assessed in the PAINDETECT questionnaire at start of treatment. We indicated this at page 17

- Etoricoxib is not available
  - In the Netherlands, Etoricoxib is available

- What of clcr cut off for NSAID, with pregabalin
  - Duloxetine and pregabalin are registered and safe to use. This is not a phase II or phase III research, but phase IV. We did not allow patients with clearance issues in the study. Creatinine levels are not checked, but renal dysfunction in history is checked, and if that is present and treatment is needed, the patient is excluded

- What of wt gain, qtc prolongation, peripheral edema, cognitive effects, memory, euphoria/recall euphoria is =30mg diazepam, pregabalin is a calcium blocker
  - Such events would be treated as medical adverse events as mentioned at page 20 in the ethical paragraph
  - We could not find the mentioning of 30 mg diazepam in our paper
  - What do you mean with your remark regarding pregabalin?
Reviewer 2:

1. Abstract – Methods/Design: The primary outcome measures should be specified
   - The primary outcome measure has been specified in the abstract

2. Background - Page 6, lines 7-8: "brain areas that are also implicated in depressive disorder and that may diminish the ability of patients to learn, and thus follow treatment properly." A reference is missing.
   - References 59 and 60 have been added

3. Methods/Design – Objectives: PHQ9: The PHQ9 is a highly specific screener for depression; However, it appears to be problematic to use a depression screener for the assessment of antidepressant effects. For this purpose, depression rating scales like the Hamilton Depression Rating Scale or the Inventory of Depressive Symptomatology are better instruments.
   - Information added that explains when response and remission for depression is achieved.
   - Furthermore, other studies in the Netherlands, with a focus on collaborative care and depression, uses the PHQ-9 as a screener and outcome measure. (see 'Moniek Vlasveld et al. 2008: Multidisciplinary Collaborative Care for Depressive Disorder in the Occupational Health Setting: design of a randomised controlled trial and cost-effectiveness study' and 'Marjolie IJf et al. 2007: Cost-effectiveness of collaborative care including PST and an antidepressant treatment algorithm for the treatment of major depressive disorder in primary care; a randomised clinical trial'). By using the PHQ9, comparisons can also be made with these studies. We did add this explanation and references to the article on page 15.

4. Exclusion of the study during the intervention phase (page 11): Do the authors use pill counts in order to answer the question whether the patients have taken at least 80% of the prescribed medication?
   - Pill counts are indeed used in every session with the psychiatrist. This has been added in the article under the heading "Exclusion of the study during the intervention phase"

5. Sample size (page 18, lines 1-2): If the authors anticipate for a possible loss to follow-up being 20%, then 3 x 79 (237) patients have to be included, not 3 x 73 (219). Figure 1 should be accordingly modified.
   - This has been modified in the text and in figure 1

6. References 10 (now reference 15) and 41 (now reference 54): Volume and pages are missing.
   - Volume and pages of these references have been added

7. References 11 and 12 are identical
   - Duplicate reference (12) has been removed

8. Reference 17 (now reference 23): The journal is missing
   - Journal has been added (as well as the missing pages)
Other changes:

- A paragraph to explain which mental health institutions participate in this study is added (page 8)

- Removed Herman Ader as author (his contribution is mentioned in the section 'Acknowledgements')

- Added the role of CFC at GGz Breburg (she facilitated and coordinates the study at GGz Breburg) (page 22)

- Added time period for the ASEC (page 20)