## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Effectiveness and cost-effectiveness of a guided internet- and mobile-based depression intervention for individuals with chronic back pain: protocol of a multi-centre randomised controlled trial |
| **AUTHORS** | Lin, Jiaxi; Sander, Lasse; Paganini, Sarah; Schlicker, Sandra; Ebert, David; Berking, Matthias; Bengel, Jürgen; Nobis, Stephanie; Lehr, Dirk; Mittag, Oskar; Riper, Heleen; Baumeister, Harald. |

## VERSION 1 – REVIEW

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| **REVIEWER** | Christopher Eccleston<br>The University of Bath, UK |
| **REVIEW RETURNED** | 01-Dec-2016 |

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| **GENERAL COMMENTS** | This is a good protocol from a strong team with a well-funded large project. There are some fixable faults.<br>1. The study has already begun, at least in recruitment. This protocol should reflect that clearly, and if possible that no randomization or treatment happened before the protocol could be changed.<br>2. A case is made in the introduction for this being the first study to combine chronic pain and depression. This is an odd claim and suggests a lack of understanding or subtlety that should be addressed. And a lack of grasp of the literature. Most chronic pain trials (see reviews) have depression as an outcome in addition to those claimed of pain and disability. And most have depression content in the treatment. Depression is a positive feature of most chronic pain presentations. I think a richer narrative is needed rather than 'I am the first to put these two things together'. This is especially true as you are including only mind and moderately depressed patients. Perhaps it is enough to say that you are keen to focus on depression as the primary outcome within this population of depressed chronic pain patients.<br>3. I would ask that you consider the endpoints again, in line with the treatment goals and content. If you are clear that this is a treatment of depression then it is depression. But if you think this a treatment of chronic pain including depression, then a trial should have the IMPACT outcome domains.<br>4. SMD for continuous variables are almost impossible to communicate. Needed are binary outcomes which exists for pain and probably for depression. The protocol should state the thresholds one needs to reach and plan to report the individual data.<br>5. Please include how missing data will be managed, and ensure that a baseline observation carry forward method will be used.<br>6. the method of blinding for randomization should be stated, and the check on its fidelity<br>7. It is very nice to see adverse events accounted for/included. |

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| **REVIEWER** | Sagar Parikh<br>University of Michigan, Ann Arbor<br>USA |
| **REVIEW RETURNED** | 20-Dec-2016 |

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| **GENERAL COMMENTS** | 1. From an ethics point of view, the way they have worded how they compensate clinics for each randomized patient makes it sound like a payment for a referral, which is explicitly forbidden by most ethics codes. It should be rephrased to indicate that participating clinics are paid for their time in participating in the research project.<br><br>2. In the CONSORT diagram, they are clear that they use online and phone administered scales to measure outcome. However, they don't say that clearly in the text; when they talk about using the HAM-D and the SCID in the text, they should specify that these are done over the phone and specify the validity of doing these clinician scales over the phone.<br><br>3. The intervention is called an "internet and mobile intervention" but they don't clarify if the intervention can actually be used on the phone, and whether the interface has been designed to read well and work well on the phone. They should specify that, and indicate how they are measuring if the participant is using a phone or a computer to access the site, since this will affect uptake and usability.<br><br>4. They should clarify if they have actually had a few patients use the new IMI and any feedback on that. It looks like they designed it and rushed it into a large trial without even a pilot validation of the intervention. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a good protocol from a strong team with a well-funded large project. There are some fixable faults.

Response: We appreciate the comment and thank reviewer 1 for reviewing the manuscript

1. The study has already begun, at least in recruitment. This protocol should reflect that clearly, and if possible that no randomization or treatment happened before the protocol could be changed.

Response: Thank you very much for this comment.

The protocol could be changed after randomisation and treatment, therefore we cannot reflect this in the manuscript. Recruitment started in October 2015, we registered this trial prior to randomisation start, documenting that the core aims and procedures have not changed in the meantime. Moreover, the present protocol was already written in a first draft version at recruitment start. Writing a well-defined protocol, taking all regulatory and good scientific practice steps into account as well as the writting-up process (commenting and approval by all co-authors) conflicted with the funding period of the project, thus we had to start randomisation prior to the acceptance of the protocol in a peer-reviewed journal. This isn´t unusual, however, still a limitation, which we discuss in the method

section.

2. A case is made in the introduction for this being the first study to combine chronic pain and depression. This is an odd claim and suggests a lack of understanding or subtlety that should be addressed. And a lack of grasp of the literature. Most chronic pain trials (see reviews) have depression as an outcome in addition to those claimed of pain and disability. And most have depression content in the treatment. Depression is a positive feature of most chronic pain presentations. I think a richer narrative is needed rather than 'I am the first to put these two things together'. This is especially true as you are including only mind and moderately depressed patients. Perhaps it is enough to say that you are keen to focus on depression as the primary outcome within this population of depressed chronic pain patients.

Response: Thank you for this comment. We revised this section to clarify that the primary outcome in our trial is depression and not pain impairment or other pain-related outcomes that have been investigated in numerous trials. We still argue, that this is the first trial examining the effectiveness of a psychological depression intervention for chronic pain patients with a depression diagnosis. This should not be mixed up with all the trials that examined pain interventions for pain patients (even with some depression treatment features as part of the pain intervention), with depression being one of several secondary outcomes and with depression being operationalized dimensionally in mixed study sample of chronic pain patients with and without elevated depression symptoms.
Indeed, different to other chronic diseases such as CAD, diabetes and cancer, there is a substantial lack of studies focusing on depression treatment in patients with chronic pain and major depression (1-5). There are three studies that examined the effectiveness of a combination therapy/collaborative care approach in this patient population (6-8), however, no study that examined the effectiveness of a psycho-social intervention for patients with chronic back pain with a confirmed depression diagnosis at baseline. As we conducted several of these systematic reviews, we are well aware of the present literature. Deducing the evidence on the effectiveness of depression treatments from pain studies with mixed depression/no-depression samples should not continue as it is currently the case.

1. Baumeister, H., Hutter, N. & Bengel, J. (2012). Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. The Cochrane database of systematic reviews, 12, CD008381.

2. Baumeister, H. & Hutter, N. (2012). Collaborative care for depression in medically ill patients. Current opinion in psychiatry, 25, 405–414.

3. Baumeister, H., Hutter, N. & Bengel, J. (2011). Psychological and pharmacological interventions for depression in patients with coronary artery disease. The Cochrane database of systematic reviews, 9, CD008012.

4. Baumeister, H. & Härter, M. (2011). Psychological comorbidity in patients with musculoskeletal diseases. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz, 54, 52–58.

5. Faller, H., Schuler, M., Richard, M., Heckl, U., Weis, J. & Küffner R. (2014). Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis. J Clin Oncol, 31, 782-793.

6. Kroenke K, Bair M, Damush T, et al. (2009) Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain. A randomized controlled trial. JAMA 301:2099-2110

7. Lin EHB, Katon W, Von Korff M, et al. (2003) Effect of improving depression care on pain and

functional outcomes among older adults with Arthritis: A randomized controlled trial. JAMA 290:2428-2434

8. Parker J, Smarr K, Slaughter J, et al. (2003) Management of depression in rheumatoid arthritis: A combined and pharmacologic and cognitive-behavioral approach. Arthritis Rheum 49:766-777

3. I would ask that you consider the endpoints again, in line with the treatment goals and content. If you are clear that this is a treatment of depression then it is depression. But if you think this a treatment of chronic pain including depression, then a trial should have the IMPACT outcome domains.

Response: Thanks for this comment. As mentioned above, the treatment we are evaluating is a depression intervention, specifically developed for individuals with chronic back pain. We revised the corresponding text passages that could be misleading. We also included several outcome domains according to the IMMPACT recommendations as secondary outcomes, such as pain intensity, pain disability and quality of life.

4. SMD for continuous variables are almost impossible to communicate. Needed are binary outcomes which exists for pain and probably for depression. The protocol should state the thresholds one needs to reach and plan to report the individual data.

Response: The gold standard for examining the effectiveness of depression interventions is depression severity based on clinical rated assessments. We follow this gold standard as defined in the study register. We agree that SMDs are difficult to interpret for clinicians, they are, however, best for between trial comparisons, as most depression trials are based on depression severity as primary outcome. Simplifying depression outcomes only to improve the communication seems inappropriate. Depression remission and response are defined as secondary outcomes, thus there are categorical outcomes, too.

5. Please include how missing data will be managed, and ensure that a baseline observation carry forward method will be used.

Response: We stated that a multiple imputation will be applied in accordance with numerous reviews stating that this can be regarded as the most robust way against biases to estimate the treatment effects. Last observation carried forward seems to be more biased. See e.g. this comprehensive review for a deeper discussion on this topic.

Schafer JL, Graham JW. Missing data: our view of the state of the art. Psychological methods 2002;7:147. http://psycnet.apa.org/journals/met/7/2/147/ (accessed 17.07.16).

6. the method of blinding for randomization should be stated, and the check on its fidelity

Response: Thanks for pointing out this important aspect. We stated that the interviewers, who assess the primary and some secondary outcomes via telephone, are blinded to the randomisation condition and specified how they remain blinded.

7. It is very nice to see adverse events accounted for/included.

Response: Thank you very much for your review!

Reviewer: 2

1. From an ethics point of view, the way they have worded how they compensate clinics for each randomized patient makes it sound like a payment for a referral, which is explicitly forbidden by most ethics codes. It should be rephrased to indicate that participating clinics are paid for their time in participating in the research project.

Response: Thanks for your suggestion to rephrase the passage. We rephrased this aspect accordingly.

2. In the CONSORT diagram, they are clear that they use online and phone administered scales to measure outcome. However, they don't say that clearly in the text; when they talk about using the HAM-D and the SCID in the text, they should specify that these are done over the phone and specify the validity of doing these clinician scales over the phone.

Response: Thanks for pointing out this important aspect. We improved the clarity in the text with regard to the assessments conducted via telephone and added in the case of the SCID information on the validity of the scales over the phone.

3. The intervention is called an "internet and mobile intervention" but they don't clarify if the intervention can actually be used on the phone, and whether the interface has been designed to read well and work well on the phone. They should specify that, and indicate how they are measuring if the participant is using a phone or a computer to access the site, since this will affect uptake and usability.

Response: Thanks for this comment. We clarified that the intervention can be used on the phone or other mobile devices with internet access. Further, we added the information that it is not possible to assess which device will be used. The intervention is primarily designed as a browser-based internet-intervention. Text messages, however, are a mobile-feature, why we name it an IMI (besides the possibility to access the intervention via mobile-devices).

4. They should clarify if they have actually had a few patients use the new IMI and any feedback on that. It looks like they designed it and rushed it into a large trial without even a pilot validation of the intervention.

Response: Thanks for this comment. We revised the passage describing the pilot validation of the intervention and some of the prior depression trials in other populations which we already conducted.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Christopher Eccleston<br>The University of Bath, UK |
| **REVIEW RETURNED** | 16-Jun-2017 |

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| **GENERAL COMMENTS** | 1. Ideally they should have agreed the full protocol before beginning, but as long as this is transparent it is not a problem. |

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| | 2. I don't agree with the resistance to report binary outcomes. The authors should consider different methods of reporting the outcomes. Doing what has been done before is not a strong defence, and communication does matter. Perhaps report both. But this is a debate probably for experts rather than a reason not to proceed with this protocol.<br><br>3. Similarly, perhaps a debate for another day, not to hold up this protocol, but the extent to which one can have a pure trial of primary depression in chronic pain patients as radically different from chronic pain patients who are depressed, is rather tenuous. And I would have thought there was much to learn from reading both literatures, and positioning the learning from this interesting trial to inform both. |

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| **REVIEWER** | Dr. Sagar Parikh<br>University of Michigan, Ann Arbor<br>USA |
| **REVIEW RETURNED** | 29-Jun-2017 |

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| **GENERAL COMMENTS** | This is a well-written, and very precise document that explains the study with great clarity. |

## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

1. Ideally they should have agreed the full protocol before beginning, but as long as this is transparent it is not a problem.

Note: Yes, we agree. We have added this to the manuscript as a limitation of the study.

2. I don't agree with the resistance to report binary outcomes. The authors should consider different methods of reporting the outcomes. Doing what has been done before is not a strong defence, and communication does matter. Perhaps report both. But this is a debate probably for experts rather than a reason not to proceed with this protocol.

Note: We do report binary outcomes (depression diagnosis, assessed by SCID for DSM), only not as the primary outcome.

3. Similarly, perhaps a debate for another day, not to hold up this protocol, but the extent to which one can have a pure trial of primary depression in chronic pain patients as radically different from chronic pain patients who are depressed, is rather tenuous. And I would have thought there was much to learn from reading both literatures, and positioning the learning from this interesting trial to inform both.
Note: Looking forward discussing these aspects maybe at one of the next pain conferences.

4. A nice job. I look forward to seeing the results. Thank you
Note: Thanks and thanks for your effort!