Author’s response to reviews

Title: Multifactorial intervention for hip and pelvic fracture patients with mild to moderate cognitive impairment: Study protocol of a dual-centre randomised controlled trial (OF-CARE)

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Author’s response to reviews:

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Dear Darren Byrne,

We want to thank for your comments and especially for your support for finalizing the manuscript. In addition, we very much appreciate the beneficial comments given by the reviewers. The comments were thoroughly reviewed and are listed point-by-point below. Adjustments were made in the manuscript or, if we disagreed on any of the comments, conclusive rebuttals are presented.

Although we had asked for it already earlier, we want to repeat our inquiry just to be sure that it will be shown correctly in the version being published: During development, submission and revision process of the manuscript I have been the responsible corresponding author (Anja Dautel). In the manuscript itself, Klaus Pfeiffer (principal investigator) is labelled as corresponding author which would be the correct allocation for the publication.

Thank you very much for processing and finalizing our revised manuscript.

Best regards,

Anja Dautel on behalf of all Co-authors

Comments Editor

1) Please indicate in the title that this is a study protocol, for example, replace "Design" with "Study protocol".

'design' was replaced by 'study protocol' (Page 1 (title), line 4).

2) Please clarify in the methods and in the Declarations section "Ethics approval and consent to participate", whether informed consent was written or verbal.

'written' was added in methods section and in Declaration section (Page 8, line 176 and Page 30, line 659).

The authors want to thank the reviewers for their beneficial comments for finalizing the manuscript. These are addressed as follows.
Comments Reviewer 1

The title describes "multifactorial intervention for osteoporotic fractures", while it is evident from the text that the project concerns only patients with fractures of hip or pelvis. Why not state this already in the title?

'osteoporotic' was replaced by 'hip and pelvic' (Page 1 (title), line 3).

Comments Reviewer 2 - Major concerns

1) It would be beneficial to the reader if the time-point comparisons for the primary outcomes were clearly defined in the primary outcomes section +/- outcomes table (not just the stats section).

Adjustments were made:

‘It is expected that the multifactorial intervention will have a beneficial impact on participants’ physical activity and functional performance between T1b and T2. Consequently, the primary outcomes include measures of these two domains’ (Page 18, line 403 to 405).

2) Based on the data analyses section, there are four primary outcomes, is this correct? (T1b compared to T2 and then T3 for both physical activity and SPPB). If this is the case, are adjustments for multiple comparisons required?

See response to comment 1 in ‘major concern’ list (2 primary outcomes) (Page 18, line 403 to 405).

3) Why was the study retrospectively registered (as per trial registration site)?

The time period between first enrolment and trial registration was one week and the reason for the slight delay of organizational nature. The registration in the German Clinical Trials Register (equivalent contents) was made prospectively (DRKS00008863, 17/7/2015). The latter was added to the manuscript (Page 4, line 87).

4) Eligibility was assessed during the first two weeks of rehab (Line 152). (A) What happens if someone is recruited during their rehab stay and then is not discharged home? (B) Are they still included in the study numbers as presumably they would have been randomised? (C) Or is
recruitment and T1a done closer to discharge? (D) If recruitment and T1a are done very close to discharge, can the readers be given a timeframe e.g. within 72h of discharge?

(A)/(B) No adjustments were made. Comment: As ‘return to home environment or assisted living’ was described as one inclusion criterion, unexpected transition to nursing home (sometimes via short term care) was a dropout-criterion. When dropped out after randomisation they are included in the study numbers. (Page 7, line 168 to 169).

(C) Adjustments were made:

‘If it was unclear that the participant could return home the final screening and recruitment procedure was postponed to the third week. Close communication was maintained with the patient, caregiver as well as rehab staff, to avoid unexpected discharge management to nursing home’. (Page 7, line 161 to 165).

(D) Explanation why timeframe for T1a was not further predefined – adjustments were made:

‘Because of very short-term decisions on reimbursement of costs for extra rehabilitation time (usually one week or some days of ambulant rehabilitation) added to the 3-week standard rehabilitation regimen it was not possible to deliver the assessment in all cases within a narrow timeframe before discharge. Otherwise these patients have had to be excluded or assessed twice within a week’ (Page 18, line 398 to 402).

5) (A) What will the assessments at T1a be used for? (B) The data analysis section suggests that for both primary and secondary outcomes T2 and T3 will be compared to T1b?

(A) Adjustments were made:

‘The assessment at T1a was performed to evaluate the further recovery process between rehabilitation and pre-intervention assessment (T1b) and to identify predictors for short-term care and nursing home transition.’ (Page 18, line 396 to 398).

(B) See response to comment 1 in ‘major concern’ list (Page 18, line 403 to 405).

6) Please consider using CACE analysis instead of per protocol.

Adjustments were made:

‘In addition to intent-to-treat and completer analyses, subgroup analyses are planned (participants with pelvic fracture, MMSE total scores < 24, fear of falling, significant depressive symptoms). Since intent-to-treat analyses may underestimate active intervention components, the
conduction of additional analyses (e.g. complier average causal effect) depending on type, randomness and degree of non-compliance is planned [87]’ (Page 26/27, line 556 to 560).

7) What subgroups will be analysed? Have these be prespecified? Has a statistical analysis plan been developed, or is statistical analysis plan planned?

See response to comment 6 in ‘major concern’ list (Page 26/27, line 556 to 560).

8) Will the primary outcome data be analysed blind to group allocation?

No, it is not planned that outcome data are analysed blind to group allocation. No adjustments were made.

Comments Reviewer 2 - General comments

1) Suggest 'fall-related hip fracture' instead of 'hip fracture after a fall' throughout the document, unless it does not work grammatically.

‘Hip fracture after a fall’ was replaced by ‘fall-related hip fracture’ (Page 5, line 107).

2) The authors have highlighted that pelvic and hip fractures may differ secondary to (non-) operative treatment in the introduction, is this one of the planned subgroups to be analysed?

See response to comment 6 in ‘major concern’ list (Page 26/27, line 556 to 560).

3) Consider replacing 'patient' with 'participant'.

’Patient’ was replaced with ‘participant’. To differentiate to also participating main caregivers, these are named as “participating caregivers”. (Continuously adjusted)

4) It is not 100% clear at what time point the T1a assessment is performed. Can the authors please clarify?

See response to comment 4 (D) in “major concern” list (Page 18, line 398 to 402).
Comments Reviewer 2 - Specific comments

1) The opening sentence could be reworded to improve readability.

The opening sentence was reworded:

‘The high incidence of fall related hip and pelvic fractures as well as the associated negative consequences have been widely described in the literature ‘ (Page 5, line 94 to 95).

2) Please include a reference for the values stated.

Reference added (‘[1]’ comment: Dyer et al. 2016, was already indicated in following sentence) (Page 5, line 98).

3) Suggest including the direction e.g. reduced pre-fracture level of functioning, reduced or impaired walking ability. Perhaps give an e.g. of fracture type.

Adjustments were made:

‘This includes high age, low pre-fracture level of functioning, reduced walking ability, high prevalence of comorbidities and certain fracture types (e.g. inter-/subtrochanteric versus cervical)’ (Page 5, line 103 to 105).

4) Suggest delete '….about the best….', because gold standard implies the best/superior quality.

‘about the best’ was deleted (Page 5, line 111).

5) This sentence could be rephrased to improve clarity. Suggest adding 'missing from the literature' or 'missing from the evidence-base'

Adjustments were made:

‘These previous results support that rehabilitation appears to be beneficial for this subgroup, in particular if it is tailored to preferences of the patients in interdisciplinary approaches [21]. However, specific interventions for cognitively impaired patients in the transition from hospital
to home which address mobility issues and the need for added support and resources (also for their caregivers) are missing from the literature so far [22]’ (Page 6, line 120 to 125).

6) Were the assessors blind to group allocation at all measurement timepoints?

Yes, assessors were blind to group allocation (Page 7, line 145), additional adjustments were made:

‘...and blind to the treatment condition’; tables 3 and 4: ‘by blinded assessors’. (Page 19, line 413; titles of table 3 and 4).

Comment: The maintenance of blinding cannot always be guaranteed, since participants might talk about the intervention during assessment appointments (home visits) and phone calls (fall evaluation).

7) Please be consistent in what you call the intervention group e.g. multifactorial.

Adjustments were made:

'exercise' was replaced by 'multifactorial intervention' (Page 7, line 146).

8) 'are' should be 'were assessed' since the dates indicate that the time has already passed; 'are' should be 'were assessed' since the dates indicate that the time has already passed.

Adjustments were made:

‘All hip and pelvic fracture patients admitted to the geriatric rehabilitation departments of the Robert-Bosch-Hospital Stuttgart and the Agaplesion Bethanien Hospital Heidelberg (both Germany) were assessed for eligibility from July 2015 to February 2018. … After medical clearing, the screening and the recruiting were planned within the first two weeks of inpatient rehabilitation and done by trained physiotherapists and sports scientists’ (Page 7, line 154 to 161).

9) Regarding the inclusion criteria 'hip or pelvic fracture within the last three months' - did the hip/pelvic fracture need to be associated with the current rehabilitation admission? Is there a chance that some participants hip/pelvic fracture may have been from a previous admission? Clarification around the 'hip or pelvic fracture within the last three months' inclusion criterion would be helpful.
Adjustments were made:

‘To include patients with complications after fracture or surgery, a maximum interval of 3 months between fracture event and admission to rehabilitation was allowed. Patients who had completed any orthopaedic rehabilitation during this time interval were not assessed’ (Page 7, line 156 to 159).

10) Suggest revise 'minimum visual acuity'. Would this be better suited to an exclusion e.g. severe vision impairment (Snellen fraction ≤20/400). Also, is this corrected or uncorrected vision?

As it was also stated as inclusion criterion in the trial registration, we would leave it unchanged ('minimal visual acuity').

Adjustments were made: 'corrected vision’ (Page 7, line 168).

11) How is the start date of the intervention determined, two to six weeks post-discharge seems like a fairly wide timeframe?

Adjustments were made:

‘This timeframe was chosen according to the experience made during piloting the interventional approach [43]. Participants of this feasibility study often needed a certain time to settle in own home environment after several weeks of acute care and rehabilitation’ (Page 10, line 214 to 216).

12) Should this read 'setting their own activity goals'?

Adjustments were made:

’their’ (Page 10, line 223).

13) How are the exercises tailored? Is this using the baseline assessment data or further assessment on visit 1?

Adjustments were made:

‘An individually tailored training schedule is compiled from a set of balance (standing, weight shifts, walking) and strength (chair rising) exercises with different intensities (table 2). For
setting the exercise plan, tasks for each exercise component are performed from easy to difficult (based on the participants’ functional capacity and according to the exercise instructor’s assessment). The exercise instructor chooses the tasks the participant is barely able to perform safely with supervision by the lay instructor. Other criteria being considered for final exercise selection are participants’ respective main and other impairments (cardio-pulmonary capacity, neurological symptoms, level of vision impairment and level of cognitive as well as mental capacity’ (Page 11/12, line 248 to 257).

14) Who the telephone calls are between could be clearer. E.g. During the 4-month intervention, the exercise instructor telephones or emails the lay instructor a minimum of five times.

Adjustments were made:

'by a minimum of…’ (Page 14, line 294).

15) This sentence could be rephrased to improve readability e.g. ‘… that has been described and successfully evaluated in previous studies conducted by our team.’

Adjustments were made:

‘The participating caregiver receives a standardized problem-solving intervention [47] including a card sorting assessment that has been described and successfully evaluated in previous studies conducted by one of the authors (KP) [30][48]’ (Page 16, line 334 to 336).

16) It would be helpful if the timepoints for the primary outcome comparisons were clearly defined. If all timepoint comparisons are made, there will be many primary outcomes.

See response to comment 1 in 'major concern' list (Page 18, line 403 to 405).

17) Suggest delete 'only'.

'only’ was deleted (Page 24, line 497).

18) To improve readability, please rephrase 'have not to show significant burden'.

Adjustments were made:
‘In contrast to own previous caregiver intervention studies [30][48], caregivers are included in this study also without showing significant burden, caregiving stress behaviours or depressive symptoms’ (Page 24, line 498 to 500).

19) Please revise 'a striven significant'.

Adjustments were made:

’an intended significant improvement’ (Page 26, line 534 to 535).

20) Which subgroups will be contrasted? Have these been prespecified?

See response to comment 6 in ‘major concern’ list (Page 26/27, line 556 to 558).

21) Consider CACE analysis instead of per protocol analysis.

See response to comment 6 in ‘major concern’ list (Page 26/27, line 556 to 560).

Table 2

1) There appears to be an accent on the ‘a’s in the intensity section.

Accents were removed.

2) For the 'Frequency' and 'Volume' sections, a total dose would be helpful for the reader. Should the 'Volume' not include the minutes? Alternatively, these sections could be combined into a 'Dose' section?

Adjustments were made in the 'Frequency' and 'Volume' section, respectively.

Table 3

1) Should adverse events be included here?

Adverse events were included in table 3.
2) For the primary outcome, it would be useful to describe the timepoint comparisons that will be made.

See response to comment 1 in ‘major concern’ list (Page 18, line 403 to 405). In table 3, no further adjustments were made.

3) It might be worth adding to the title that the assessors were blind to group allocation?

Information about assessors blinded to group allocation was added to the titles of table 3 and 4, respectively.

Table 4
1) Was there any attempt to measure the impact of caring for a person with dementia?

Adjustments were made at table 4:

The also informally evaluated time burden of participating caregivers (average duration/day and number of days at T1b, T2 and T3) was added to the table (outcome ‘Others’). It includes three dimensions of care: ‘1. body care, nutrition, mobility 2. household help IADLs (e.g. housekeeping) 3. additional supervision’.

Comment: For more detailed information it is referred in the manuscript to Pfeiffer et al. (Page 25, line 508 to 509).

Figure 1
1) At what point in rehab is T1a performed?

See response to comment 4 in ‘major concern’ list (Page 18, line 398 to 402) and added figure legend.

2) The timeframe between discharge and T1b assessment and the intervention would be useful to add to the figure.

The timeframe between discharge and T1b was added in the figure legend. No adjustments were made in the figure.
3) Please spell out the abbreviations in the figure legend so that the figure can standalone e.g. T1a. Alternatively, label the T1a, T1b, T2, T3 as assessments conducted by assessors’ blind to group allocation.

A figure legend for the abbreviations T1a, T1b, T2, T3 was added.