**Introduction**

Multidisciplinary rehabilitation is recommended as a second-line treatment for patients with chronic low back pain who do not respond to first-line treatments1, 2. Multidisciplinary rehabilitation is a multifaceted intervention targeting the wide range of modifiable factors known to contribute to chronic low back pain and it is usually based on the widely accepted biopsychosocial approach1-4. There are different ways of delivering multidisciplinary rehabilitation. A Cochrane review included 12 randomised controlled trials comparing at least two different multidisciplinary rehabilitation approaches3, but it did not compare the effectiveness of different delivery modes. Thus, the optimal approach, dose, content or structure of a multidisciplinary rehabilitation programme is not known3.   
 To optimize the effectiveness of multidisciplinary rehabilitation, it is generally considered important for the patient to integrate the new knowledge, skills and behaviours gained from an inpatient rehabilitation programme into their daily life. Approaches to support this integration include taking the patient’s environment into account5, 6 and ensuring regular interaction over time between the patient and the multidisciplinary team via scheduled booster sessions7. One trial included in the Cochrane review3 assessed the effect of adding booster sessions (phone calls) to a 4-week inpatient rehabilitation programme8. The trial found a small, but not statistically significant benefit compared with the same inpatient rehabilitation programme without booster sessions8.   
 From a theoretical point of view, it seems reasonable to combine the biopsychosocial approach5, 9 with the Chronic Care Model7 in terms of supporting integration of knowledge, skills and behaviours gained from an inpatient rehabilitation programme into the patient’s own environment and daily life10.   
No trials have yet tested whether an approach like that is more effective than an existing inpatient rehabilitation programme. Therefore, we designed an integrated multidisciplinary rehabilitation programme (integrated programme) that comprised a 2-week inpatient stay, followed by home-based activities plus two further inpatient booster sessions (each lasting 2 days)10. We hypothesised that the integrated programme, combining inpatient interventions supported by a multidisciplinary team with home-based activities to better integrate knowledge, skills and behaviours in the patient’s daily life, would be superior to an existing multidisciplinary inpatient rehabilitation programme (existing programme).   
 Therefore, in patients with chronic low back pain, the aim of this trial was to compare the effectiveness of the integrated programme with the existing programme in terms of back-specific disability.

**Methods**

The Central Denmark Region Committees on Biomedical and Research Ethics approved the trial (journal number: 1-10-72-117-16), and the trial was registered (ClinicalTrials.gov; identifier NCT02884466). The trial was funded by Sano, Aarhus University, the Danish Rheumatism Association, and Familien Hede Nielsens Fond, and reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement11.   
 A consultative and collaborative approach was used when involving stakeholders (patients, providers, administrative and management staff) in the development, feasibility-testing and evaluation of the trial. The short form of “Guidance for Reporting Involvement of Patients and the Public”12 was used to structure the reporting of patient and public involvement (Additional file 1). A process evaluation was integrated into the trial as advocated for complex interventions13 (Additional file 2).  
 This was a single-centre, pragmatic, two-arm parallel randomised controlled trial conducted in a rheumatology rehabilitation centre in Aarhus, Denmark10. Patients were referred to the rehabilitation centre where the trial was conducted from general practitioners or hospital departments10. Rheumatologists at that centre identified potentially eligible patients based on the clinical problem detailed on the referral request and a list of ICD-10 diagnosis codes for diseases, signs and symptoms related to chronic low back pain. Before inclusion, a research assistant performed eligibility checks by telephoning potentially eligible patients. Written information and an informed consent form were e-mailed by the research assistant, and if a signed version was returned, the patient was included. Patients then waited until the next available rehabilitation programme group was scheduled, as this is usual practice at the centre. The final eligibility checking was performed by rheumatologists on the first inpatient day.   
 Patients were eligible if they had chronic low back pain for more than 12 months (with or without sciatica and/or with or without widespread pain) and if they were 18 years or older. The exclusion criteria were: 1) severe systemic diseases (American Society of Anesthesiologists Physical Status classification system > 314), 2) a diagnosis of axial spondyloarthritis, 3) spinal fracture within the last 3 months, 4) severe osteoporosis, 5) active cancer, 6) severe psychiatric disease, 7) pregnancy, 8) lack of fluency in Danish, and 9) minimal back-specific disability (Oswestry Disability Index score < 2115).  
 A computer-generated randomisation with 1:1 allocation in random blocks of six ensuring allocation concealment was performed by the research assistant. Randomisation was stratified on the basis of disability at baseline using the Oswestry Disability Index score with cut-off at 4115 in order to achieve approximate balance in mean disability levels in the arms of the trial. The research assistant informed patients about intervention allocation and the dates for their allocated rehabilitation programme. Blinding of patients and providers was not possible due to the nature of the interventions. In order to ensure patients had equal expectations about each rehabilitation programme, we attempted to blind participants to the hypothesis by informing them that the trial aimed to compare two rehabilitation programmes that meet current recommendations1, 2. The researcher who performed the statistical analysis was blinded.   
 A secure electronic database was used to e-mail questionnaires and store data. Patients were e-mailed the questionnaires 10 days prior to the inpatient stay. A reminder was e-mailed after 5 and 8 days if required. If they were not completed, the research assistant ensured completion of questionnaires on an electronic tablet on the first inpatient day. Patients who were unable to complete the electronic questionnaires completed a paper version.   
 Patients excluded between baseline and before the start of their rehabilitation programme (due to exclusion criteria), patients who, following baseline, subsequently reported they did not wish to participate, or patients who dropped out of their rehabilitation programme, did not receive further questionnaires.   
 Demographic data were collected at baseline. The outcome measures were collected: 1) before randomisation (baseline), 2) before the start of the rehabilitation programme, and 3) at the 26-week follow up (26 weeks after the start of the rehabilitation programme).   
 The choice of outcome domains and outcome measures was based on patient and public involvement in combination with international recommendations16-18. The primary outcome was back-specific disability assessed by the Oswestry Disability Index version 2.1a15. Secondary outcomes were back pain intensity assessed by a Numerical Rating Scale 18, pain self-efficacy measured by the Pain Self-Efficacy Questionnaire19, Health-related Quality of Life measured by the EQ-5D 5L ©20, depression measured by the Major Depression Inventory21 and physical activity assessed by three questions22.   
 Cases of adverse events and death were collected from the electronic health records. Adherence was extracted from the electronic health records and defined as attending ≥ 80% of the scheduled inpatient days. Thus, adherence was defined as attending ≥ 17 inpatient days in the existing programme and attending ≥ 12 inpatient days in the integrated programme. Adherence to the home-based activities was not assessed. In brief, both rehabilitation programmes comprised multidisciplinary inpatient rehabilitation based on the biopsychosocial approach and included the same 38 clinical activities, the same providers and the same contact hours between patients and providers. An inpatient day consisted of 8-10 hours per day alternating between 1) group lecture and dialogue, 2) supervised group sessions, 3) unsupervised group sessions, 4) individual counselling and 5) unsupervised individual exercise. Full details about clinical activities, providers and setting have been described previously10. The key difference between the two rehabilitation programmes was in the way in which they were delivered.   
 Patients in *the integrated programme* participated in: 1) pre-admission day, 2) 2-week home-based activities, 3) 2-week inpatient stay, 4) 4-week home-based activities, 5) first 2-day inpatient booster session, 6) 6-week home-based activities, 7) second 2-day inpatient booster session, and 8) 26-week follow up (a total of 15 inpatient days) (Figure 1). The integrated programme was developed and feasibility-tested according to the Medical Research Council’s guidance on developing and evaluating complex interventions13 as previously described10.   
 Patients in *the existing programme* were offered a 4-week inpatient stay and 26-week follow up (a total of 21 inpatient days). The existing programme has been usual practice for more than 15 years in the setting under study.

[Insert Figure 1.]

**Statistical analysis** The sample size calculation was based on a hypothesis of superiority of the integrated programme over the existing programme for back-specific disability (using the Oswestry Disability Index). A difference of 4 points has been suggested as a minimum clinically important difference15. The trial was powered to be able to detect a standardised mean difference of at least 0.5 between the rehabilitation programmes, assuming a decrease of 10 points on the Oswestry Disability Index at 26 weeks follow up in the integrated programme compared with a decrease of 5 points in the existing programme. The standard deviation was informed by our previous feasibility study with 12 patients attending the existing programme (standard deviation of 10). With 80% power and a significance level of 0.05, 64 patients were required in each arm of the trial, and allowing for a loss to follow up of 20%, a total of 160 patients was needed.  
 A statistical analysis plan was completed prior to data analyses. Baseline demographic and clinical characteristics were descriptively summarised and presented as the mean (standard deviation (SD)), median (inter-quartile range) or number (%) according to patients allocated at baseline and patients providing 26-week follow up. Additionally, differences in sex, age and ICD-10 diagnosis codes are presented for those patients randomised and those declining to participate. The primaryanalysis was a modified intention-to-treat analysis according to originally allocated intervention arms, excluding patients with missing outcome data at the 26-week follow up (=complete case analysis). The between-group difference in change scores from baseline to the 26-week follow up was analysed by multiple linear regression for continuous outcomes using change scores as the dependent variable, rehabilitation programme as the independent variable, and the corresponding baseline score as a covariate. Categorical outcomes were compared using Wilcoxon Rank-Sum Tests. For the secondary analysis, the within-group changes from baseline to the 26-week follow up were presented descriptively. Furthermore, the robustness of the modified intention-to-treat analysis in terms of the primary outcome was checked by an intention-to-treat analysis using imputed data with the last value carried forward. A per-protocol analysis was also conducted excluding patients with low adherence to their rehabilitation programme (defined as <80% attendance). An exploratory analysis including waiting time (days between randomisation (baseline) and the start of the rehabilitation programme) as a covariate was performed, as the process evaluation revealed that this variable by chance differed between the two rehabilitation programmes. P values ≤ 0.05 were considered statistically significant. For statistical analysis, STATA 15 was used.

**Results**

Participant recruitment started in February 2016 and ended in August 2018. The first rehabilitation programme commenced in September 2016 and the last rehabilitation programme reached the 26-week follow up in May 2019. The flow of participants is shown in Figure 2. The 71 patients who declined to participate did not differ from those willing to participate with respect to age (mean age 50, age range 22-79), sex (68% women) or diagnosis (data not presented). Baseline demographic and clinical characteristics were comparable between arms (Table 1). Adherence to the inpatient days (those attending ≥ 80%) was excellent in both arms of the trial (100% in the existing programme; 99% in the integrated programme). Mean waiting time was 141 days (SD 10) in the existing programme and 105 days (SD 9) in the integrated programme. There were no related adverse events or deaths.

[Insert Figure 2.]

[Insert Table 1.]The Oswestry Disability Index scores decreased on average in those allocated to the integrated programme from 41 (SD 11) at baseline to 36 (SD 14) at the 26-week follow up, and in those allocated to the existing programme from 43 (SD 12) at baseline to 37 (SD 16) at the 26-week follow up. The adjusted between-group difference was -0.28 (95% confidence interval; -4.02, 3.45) which was neither statistically nor clinically significant (Table 2). Data on physical activity were not presented as the analysis revealed low quality of the data.

[Insert Table 2.]   
No statistically significant differences were found between the rehabilitation programmes in any of the secondary outcomes (Table 2). The data in Table 2 show that, on average patients in both arms of the trial improved from baseline to the 26-week follow up on all outcomes. Intention-to-treat analysis with the last value carried forward did not change the conclusions from the primary analysis (data not presented).As only one patient had poor adherence (attending < 80% of the inpatient days), the per-protocol analysis was deemed unnecessary. The exploratory analysis, including waiting time as a covariate, did not change the trial conclusion (data not presented).

**Discussion**This trial provides convincing evidence that changing the way in which a multidisciplinary rehabilitation programme is delivered by alternating inpatient stays with home-based activities and booster sessions, did not lead to better outcomes for patients allocated to an integrated programme compared with patients allocated to an existing programme at the 26-week follow up. As expected, given existing clinical practice guidelines1, 2 and systematic review evidence3, on average, patients in both rehabilitation programmes improved over time.   
 There are several potential reasons for our results. One explanation relates to the lack of sufficient difference between the two rehabilitation programmes in the trial. The clinical activities and contact hours with the providers were the same in the two rehabilitation programmes; the key difference was the way in which the rehabilitation programmes were delivered. Furthermore, the process evaluation revealed difficulties with implementing elements of the integrated programme. In order to support integration of knowledge, skills and behaviours into daily life, patients in the integrated programme received a preparation pamphlet as well as a phone call before each booster session10. The pamphlet was requested and developed by the providers delivering the rehabilitation programmes, but despite that, the pamphlet was infrequently provided to patients, and instruction in, and follow-up on, patient’s reflections reported in the pamphlet was often forgotten. The providers mentioned lack of time and unclear responsibility for conducting the phone calls as possible barriers to implementation. The implementation difficulties could potentially have served to attenuate any difference in outcomes between the two rehabilitation programmes, as these elements were essential parts of the integrated programme.   
A further explanation for the results relates to the Oswestry Disability Index as the primary outcome measure. The Oswestry Disability Index is a measure of back-related disability and is not a measure of successful integration of knowledge, skills and behaviours in the daily life of patients, which was the intended target of the integrated programme. As a measure of disability, the Oswestry Disability Index was expected to be a proxy for this integration, but the relationship between disability and integration of knowledge, skills and behaviours is unknown. The reasons for choosing the Oswestry Disability Index as the primary outcome measure were a combination of patient and public involvement and international recommendations about core outcome sets for trials in the field of low back pain16-18. On the other hand, the domain of pain self-efficacy may be somewhat closer to the domain of integrating knowledge, skills and behaviours. However, we also observed no difference between the arms of the trial on this outcome, although we did not power the trial to detect differences on this outcome. To our knowledge, no single outcome measure has been developed and validated to measure the domain of integrating knowledge, skills and behaviours into daily life.   
 We identified three further trials23-25 in addition to the12 trials already included in the most recent Cochrane review3 that compared two or more multidisciplinary rehabilitation programmes. Of all 15 trials identified, only two used the Oswestry Disability Index as their primary outcome measure24, 25. The changes they observed in back-specific disability are similar to those we observed with a within-group decrease of between 7-9 points at the 12-week follow up24 and a within-group decrease between 2-5 points at the 52-week follow up25. Neither of these trials found significant between-group differences24, 25, similar to our results.   
 There are conflicting results of adding booster sessions to interventions for musculoskeletal pain. Only one trial involving patients with chronic low back pain has assessed the effect of booster sessions and found no additional benefit8. A review including three trials26 and a further single trial27 in patients with hip and/or knee osteoarthritis, showed beneficial effects of adding booster sessions to exercise therapy. The opposite was found in two other trials with patients with hip and/or knee osteoarthritis28, 29. These conflicting results question the effectiveness of adding booster sessions.

The strengths of this trial include the randomised parallel design, comparability of patients in the two arms at baseline, and high adherence to the scheduled inpatient days. We also reached our target sample size and had high follow-up rates. A small proportion of patients did not complete the trial (12 out of 82/83≈15%), the majority of whom disengaged from the trial before the start of their rehabilitation programme (7 out of 12=58%), largely due to the waiting time. Those patients not completing the programme were balanced in numbers and baseline characteristics between the two arms. The thorough development and feasibility-testing of the integrated programme according to the Medical Research Council’s guidance for complex interventions13, including patient and public involvement (Additional file 1) as well as the integrated process evaluation (Additional file 2) are considered further strengths.   
 The trial also had some limitations. The lack of measurement of adherence to the home-based activities is a limitation. Data on adherence to home-based activities could have allowed us to better assess if the hoped-for integration of knowledge, skills and behaviours was different in patients in the integrated programme compared with those in the existing programme. Measuring adherence to home-based activities is a methodological challenge hence we opted to simply capture data on inpatient attendance. A second limitation is the potential risk of contamination. Both rehabilitation programmes were managed by the same providers, in the same centre and at the same time, meaning that patients inevitably met each other. Thus, both the patients and the providers would have had the opportunity to compare and discuss the two rehabilitation programmes allowing for patients in the existing programme to potentially be inspired to integrate knowledge, skills and behaviours in their daily life, diluting any differences between the two rehabilitation programmes. Finally, it is considered a limitation that a cost-utility analysis was not conducted.

This trial has contributed new knowledge regarding the delivery of rehabilitation programmes; as long as the content is the same, it appears that the way in which a rehabilitation programme is delivered does not impact clinical outcomes at least in the medium term as assessed in this paper. Given this, factors such as patient preferences and/or the costs of the different rehabilitation programmes should perhaps drive decisions about the delivery approach. Patients, clinicians, researchers and stakeholders need to continue to collaborate about development, evaluation and implementation of effective second-line treatments for patients with chronic low back pain. Future research needs to investigate the long-term outcomes from different approaches to the delivery of rehabilitation programmes.

**Clinical message**

Introducing an integrated rehabilitation programme aiming to better integrate new knowledge, skills and behaviours into the daily life of the patient with chronic low back pain, did not lead to better back-related disability compared with an existing rehabilitation programme at the 26-week follow up.

Patients in both rehabilitation programmes reported improvements in the primary outcome (disability) over the 26 weeks, and those improvements were of clinically relevant size.

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