Comparison of two multidisciplinary rehabilitation programmes in patients with chronic low back pain - A randomised controlled trial

PhD dissertation

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List of scientific papers

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Study 1

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The Sano study: justification and detailed description of a multidisciplinary biopsychosocial rehabilitation programme in patients with chronic low back pain.
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Study 2

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The effect of an integrated multidisciplinary rehabilitation programme alternating inpatient interventions with home-based activities for patients with chronic low back pain: a randomized controlled trial.
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Study 3

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The effect of an integrated multidisciplinary rehabilitation programme for patients with chronic low back pain: long-term follow up of a randomised controlled trial.
Submittet to Clinical Rehabilitation March 2020.

The studies are found in Appendices 1-3.

List of abbreviations

CERT: Consensus on Exercise Reporting Template

CI: Confidence Interval

CLBP: Chronic Low Back Pain

CONSORT: Consolidated Standards of Reporting Trials

CReDECI 2: Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline

EQ-5D 5L: EuroQol-5 Domain 5-level

GRIPP-2: Guidance for Reporting Involvement of Patients and the Public 2

HRQoL: Health Related Quality of Life

ICD-10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems

ICF: International Classification of Functioning, Disability and Health

ITT: Intention-To-Treat

LBP: Low Back Pain

MDI: Major Depression Inventory

MRC: Medical Research Council

NRS: Numeric Rating Scale

ODI: Oswestry Disability Index

PPI: Patient and Public Involvement

PRECIS-2: Pragmatic Explanatory Continuum Indicator Summary (second version)

PSEQ: Pain Self-Efficacy Questionnaire

RCT: Randomised Controlled Trial

SD: Standard Deviation

TIDieR: Template for Intervention Description and Replication

WHO: World Health Organization

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Summary

Background

Low back pain (LBP) is a substantial burden worldwide constituting the most frequent cause of years lived with disability and having an enormous impact on individuals affected, their relatives and society in general. Reasons for the development and persistence of chronic LBP (CLBP) and related disability include a complex interaction between multiple biopsychosocial factors. Thus, a biopsychosocial approach is recommended when guiding management of patients with CLBP, and therefore, recent evidence-based clinical practice guidelines in the CLBP area recommend the biopsychosocial model to inform clinical practice. Those evidence-based clinical practice guidelines recommend multidisciplinary rehabilitation as one of the possible second-line treatment options for patients with CLBP. However, the optimal dose, content or delivery of such multidisciplinary rehabilitation programmes remains unknown. Against this backdrop, an integrated programme was developed, feasibility-tested and evaluated. Thus, the aims of this dissertation were: 1) to justify and describe the integrated programme, 2) to compare the effectiveness of the integrated programme with an existing programme at the 6-month follow up, and 3) to compare the effectiveness of the integrated programme with an existing programme at the 12-month follow up.

Methods

In Study 1, the Template for Intervention Description and Replication (TIDieR) checklist was used as a structural framework for the description of the integrated rehabilitation programme. As part of the description, the Medical Research Council's guidance, 'Developing and evaluating complex interventions', was used as a framework to justify the integrated rehabilitation programme. The process was underpinned by patient and public involvement.

In Studies 2 and 3, a single-centre, pragmatic, two-arm parallel, randomised controlled trial (RCT) was conducted in a Danish rheumatology inpatient rehabilitation centre. Adults with CLBP for more than 12 months were randomly allocated, using computer-generated randomisation (1:1 ratio) to the integrated programme or to the existing programme. The integrated programme comprised a pre-admission day, 2 weeks at home preparing for the next inpatient stay, 2 weeks as an inpatient followed by home-based activities plus two 2-day inpatient booster sessions, and a 6-month follow up visit, whereas the existing programme comprised a 4-week inpatient stay, and a 6-month follow up visit. Patient-reported outcomes were collected at baseline, 6-month follow up (Study 2) and 12-month follow up (Study 3). The primary outcome was disability measured by the Oswestry Disability Index (ODI). Secondary outcomes included pain intensity (Numerical Rating Scale), pain self-efficacy (Pain Self-Efficacy Questionnaire), health-related quality of life (EQ-5D),

and depression (Major Depression Inventory). In Study 2, a complete case analysis was performed using linear regression, and in Study 3, analysis was by intention-to-treat, using linear mixed models.

A process evaluation using both qualitative and quantitative methods was nested into the RCT.

Results

In Study 1, the integrated programme was justified and described in detail. The inpatient part of the programme consisted of 38 clinical activities, some of them delivered more than once. The 38 clinical activities were described in an activity sheet developed for this purpose, combining five items from the TIDieR checklist.

In Studies 2 and 3, between February 2016 and August 2018, 303 patients were assessed for eligibility. Of them, 165 patients (mean age: 50 years (SD 13) with mean ODI score of 42 (SD 11)) were randomised, 82 patients to the integrated rehabilitation programme and 83 patients to the existing programme. Baseline characteristics were comparable between programmes.

In Study 2, 139 patients (70 from the integrated programme and 69 from the existing programme) provided 6-month follow-up data. The between-group difference in the ODI score was −0.28 (95% CI: −4.02; 3.45), which was neither statistically nor clinically significant. No significant differences were found in the secondary outcomes.

In Study 3, the between-group difference in the ODI score was -0.53 (95% CI: -4.08; 3.02) at the 12-month follow up, being neither statistically nor clinically significant. No significant differences were found in the secondary outcomes.

Conclusion

The integrated programme for patients with CLBP was justified and described. The intervention description was used for structuring and standardising the content and delivery of the integrated programme in the RCT. The integrated programme did not lead to improved back-specific disability or other outcomes for patients with CLBP when compared with the existing programme at 6-month and 12-month follow up. The null effect may be due to the identical comprehensive nature of the two rehabilitation programmes being compared, the continuous organisational challenges attenuating any difference between the two rehabilitation programmes or a number of other reasons.

Dansk resumé

Baggrund

Lænderygsmerter er en meget udbredt helbredstilstand på verdensplan. Samtidig er det den hyppigste årsag til leveår med påvirket funktionsevne, og det har en væsentlig indflydelse på personen, der lider af lænderygsmerterne, deres pårørende og samfundet generelt. Et komplekst sammenspil mellem biopsykosociale faktorer anses som årsag til udvikling og kronificering af lænderygsmerter (kroniske lænderygsmerter) og den afledte nedsatte funktionsevne. Af samme grund bygger de seneste evidensbaserede kliniske retningslinjer inden for dette område også på en anbefaling af en biopsykosocial tilgang i klinisk praksis. I de evidensbaserede kliniske retningslinjer anbefales tværfaglig rehabilitering som en af de mulige anden valgs behandlinger til patienter med kroniske lænderygsmerter, der ikke responderer på førstevalgs behandling. Den optimale dosis, det optimale indhold og den optimale opbygning af et sådant tværfagligt rehabiliteringsprogram er fortsat ukendt. På baggrund heraf blev et integreret program udviklet, testet og evalueret, hvorfor formålet med denne afhandling var: 1) at underbygge og beskrive det integrerede program, 2) at undersøge effekten af det integrerede program sammenlignet med et eksisterende program efter 6 måneder, og 3) at undersøge effekten af det integrerede program sammenlignet med et eksisterende program efter 12 måneder.

Metode

I Studie 1 blev tjeklisten the Template for Intervention Description and Replication (TIDieR) brugt til at strukturere beskrivelsen af det integrerede program. Som en del af beskrivelsen blev også the Medical Research Council's guidance om udvikling og evaluering af komplekse interventioner brugt som rammeværk i forhold til at understøtte rationalet for det integrerede program. Processen blev underbygget ved at involvere patienter og øvrige samarbejdspartnere.

Studie 2 og 3 var et pragmatisk randomiseret kontrolleret studie (RCT) med to parallelle grupper udført på et dansk reumatologisk rehabiliteringscenter. Voksne med kroniske lænderygsmerter i mere end 12 måneder blev ved hjælp af computergenereret randomisering tilfældigt fordelt (1:1 ratio) til det integrerede program eller det eksisterende program. Det integrerede program bestod af en forundersøgelsesdag, 2 uger hjemme med forberedelse til det næste forløb, 2 ugers indlæggelse efterfulgt af aktiviteter i hjemmet plus 2 gange booster sessioner af to dages varighed. Programmet blev afsluttet med opfølgning efter 6 måneder. Det eksisterende program bestod af fire ugers indlæggelse og blev afsluttet med opfølgning efter 6 måneder. Patientrapporterede målemetoder blev anvendt til at indsamle data ved baseline, samt 6 måneder (Studie 2) og 12 måneder (Studie 3) efter interventionsstart. Det primære outcome var funktionsevne målt med Oswestry Disability Index (ODI). Sekundære outcomes var smerte intensitet (Numerisk Rang

Skala), smerte self-efficacy (Pain Self-Efficacy Questionnaire), helbredsrelateret livskvalitet (EQ-5D) og depression (Major Depression Inventory). I Studie 2 blev en complete-case analyse udført ved hjælp af lineær regression. I studie 3 blev en intention-to-treat analyse udført ved hjælp af lineær mixed models.
En procesevaluering der brugte både kvalitative og kvantitative metoder blev gennemført sideløbende med RCT'et.

Resultater

Rationalet for det integrerede program blev underbygget, og programmet blev beskrevet i detaljer (Studie 1). Programmet bestod af 38 forskellige kliniske aktiviteter, hvoraf nogle af dem blev leveret mere end en gang. De 38 kliniske aktiviteter blev beskrevet i et aktivitetsskema udviklet til samme formål og bestod af fem punkter fra TIDieR tjeklisten.

Studierne 2 og 3 blev udført i perioden fra februar 2016 til august 2018. 303 patienter blev undersøgt med henblik på om de opfyldte in- og eksklusionskriterierne. Af dem blev 165 patienter randomiseret (mean alder var 50 år (SD 13) og mean ODI score var 42 (SD 11)), hvoraf 82 patienter blev tildelt det integrerede program og 83 patienter det eksisterende program. Demografiske og kliniske karakteristika var sammenlignelige mellem de to programmer ved baseline.

I Studie 2 bidrog 139 patienter (70 fra det integrerede program og 69 fra det eksisterende program) med data. Forskellen mellem grupperne i ODI score var −0,28 (95% CI: −4,02; 3,45) efter 6 måneder, hvilket hverken var statistisk eller klinisk signifikant. Der blev ikke fundet signifikant forskel mellem grupperne på nogle af de sekundære outcomes.

I Studie 3 var forskellen mellem grupperne i ODI score -0,53 (95% CI: -4,08; 3,02) efter 12 måneder, hvilket hverken var statistisk eller klinisk signifikant. Der blev ikke fundet signifikant forskel mellem grupperne på nogle af de sekundære outcomes.

Konklusion

Et integreret program til patienter med kroniske lænderygsmerter blev underbygget og beskrevet. Beskrivelsen af interventionen blev brugt til at strukturere og standardisere indholdet og opbygningen af det integrerede program i RCT'et. Sammenlignet med deltagelse i det eksisterende program medførte deltagelse i det integrerede program ikke forbedret funktionsevne eller andre outcomes hos patienter med kroniske lænderygsmerter. Dette gjaldt både sammenligningen foretaget ved 6 og 12 måneder. Flere årsager kan forklare den manglende forskel, herunder at de to programmer var for ens og at de organisatoriske udfordringer medførte at forskellen mellem de to programmer blev udvisket.

1. Background

1.1 The burden of low back pain

Low back pain (LBP) is a highly prevalent health condition affecting more than 540 million people worldwide (1). Moreover, it constitutes the most frequent cause of years lived with disability (1). LBP has substantial impacts on individuals, families, communities and health care systems, as well as its societal costs due to work absenteeism and its associated effects on the social support system (2, 3).

LBP is defined by the location of pain on the posterior aspect of the body below the costal margin and above the inferior gluteal folds, and it can be accompanied by pain in one or both legs (sciatica) (2-4). The prevalence and burden of LBP increases with age (2, 5), and LBP is more common in women than in men (2). The majority of patients have non-specific LBP, meaning that no underlying pathology or cause can be identified, and often concurrent pain is present elsewhere in the body (2, 3). LBP with a pain duration persisting for more than three months is often defined as chronic LBP (CLBP) (2-4). A minority of an estimated 10-15% of patients with LBP develops CLBP (2, 3, 6), and they comprise the group of patients with LBP bearing the greatest proportion of the disease burden (3, 6-8).

Reasons for the development and persistence of LBP and related disability include a complex interaction between biophysical factors, genetic factors, psychological factors, social factors, lifestyle factors, and comorbidities (2-4, 9, 10). The contribution of these different factors varies from individual to individual (8), and over time (6). Besides pain and disability, patients with LBP often experience psychological consequences with signs of anxiety and depression, and reduced quality of life (2, 3, 7). Furthermore, negative consequences can be experienced for social life including leisure, and work life (2, 3, 7).

In light of the biopsychosocial influence on the development and persistence of LBP and related disability, some elaboration on the biopsychosocial approach, that allows for and incorporates all the biophysical, psychological, and social factors, is needed.

1.2 The biopsychosocial approach

In 1977, George Engel described the biopsychosocial model (11), and 10 years later, Gordon Waddell suggested the model as a new theoretical framework for the understanding and management of LBP (12). This contributed to a fundamental change in the existing approach to LBP (12, 13), and nowadays, the biopsychosocial approach is still widely recognised as the dominant one in the understanding and management of LBP and related disability (2, 3, 6, 8, 13-15).

Years later, in 2001, the biopsychosocial model formed the basis of the International Classification of Functioning, Disability and Health (ICF), published by the World Health Organisation (WHO) (16). ICF is the international standard to describe and measure health and disability; it focuses on functioning and disability, and how these are influenced by contextual factors (16), and it seeks to capture how people with a specific health condition function in their daily life (17).

More recently, leading proponents, for example the alliance behind the third edition of the White Book on Physical and Rehabilitation Medicine in Europe, and four editorials in the journal Clinical Rehabilitation, have endorsed the biopsychosocial model as a rational approach to rehabilitation (15, 17-20).

In the field of LBP, the biopsychosocial approach is recommended when guiding management of patients in view of the key contributors to LBP and related disability (2, 3, 6, 14, 21). Therefore, recent evidence-based clinical practice guidelines in the CLBP field recommend the biopsychosocial approach to inform clinical practice (22-24).

1.3 Management of patients with CLBP

The aforementioned recent evidence-based clinical practice guidelines endorse education and self-care (including advice to remain active and patient education), and non-pharmacological therapy (including exercise therapy and cognitive behavioural therapy) as first-line treatment options for patients with CLBP (14, 22, 23). Multidisciplinary rehabilitation is recommended as one of the possible second-line treatment options for patients who experience disability due to CLBP and who are not responding to first-line treatments (3, 14, 22-24).

The recommendations about multidisciplinary treatment in recent evidence-based clinical practice guidelines (14, 22-24) are based on research including a Cochrane systematic review and meta-analysis aimed at assessing the long term effects of multidisciplinary rehabilitation for patients with CLBP (7). In total, 41 RCTs including 6858 participants comparing multidisciplinary rehabilitation with usual care, physical treatment, surgery and waiting list, respectively, were included (7). In total, 16 RCTs provided moderate quality evidence that multidisciplinary rehabilitation was more effective than usual care in terms of decreasing pain and disability (7). Furthermore, 19 RCTs provided low quality evidence that multidisciplinary rehabilitation was more effective compared with physical treatments in decreasing pain and disability (7). The effect lasted longer than 1 year regardless of the comparator being either usual care or physical treatments (7). Additionally, 12 RCTs comparing two or more multidisciplinary rehabilitation programmes were identified but not included in a comparative effectiveness analysis, as this did not inform the main research question of the review (7). Thus, the optimal dose, content or delivery of a multidisciplinary rehabilitation programme remains unknown (7).

1.4 Multidisciplinary rehabilitation - a complex intervention

Several formal definitions of the concept rehabilitation exist (25, 26). According to the World Report on Disability, produced jointly by WHO and the World Bank, rehabilitation is defined as *"a set of measures that assist individuals who experience, or are likely to experience, disability to achieve and maintain optimal functioning in interaction with their environments"* (27).

Rehabilitation is a problem-solving process (17, 28, 29) aimed at optimising functioning and minimising disability of people with a given health condition (17, 20, 27, 30) enabling them to continue with their lives (6). The process of rehabilitation is described as dynamic and iterative, encompassing the following four actions: 1) assessment, 2) goal-setting, 3) intervention, and 4) evaluation (15, 17, 19, 27, 29, 31).

When used in this dissertation, multidisciplinary rehabilitation is defined as detailed in the aforementioned Cochrane review (7). The premise is that multidisciplinary rehabilitation is characterised in accordance with the biopsychosocial approach, the intervention involves a physical component and a psychological and/or social/work targeted component, it is delivered by more than one profession, the intensity and approach varies, and it can be provided in inpatient- or outpatient settings (7).

In general, health care interventions cover a wide range of complexity and there is no clear cut-off between simple and complex interventions (32). However, when imagining health care interventions as a hierarchy of complexity, management of patients with disability is near the top. Rehabilitation interventions are thought of as complex interventions (15, 19, 28, 33) because they:

- Involve several providers from different professions within different teams, organisations, and sectors (17, 19, 27, 31, 33, 34)
- Usually consist of several or many primary interventions aimed at different parts of the biopsychosocial approach (15, 17, 27-29, 33)
- Use a person-centered approach by tailoring the rehabilitation intervention to the needs, goals and preferences of the patient (17, 27, 28, 33, 35)
- Pay attention to and acknowledge the context (15, 17, 28, 33, 35)

Several of the abovementioned aspects of rehabilitation are similar with dimensions defining complex interventions (32).

Summing up, the burden of LBP is indisputable, and it is well established that the development and persistence of LBP and associated disability is attributed to a complexity of biopsychosocial factors. Multidisciplinary rehabilitation is a complex intervention targeting the wide range of modifiable factors known to contribute to CLBP and it is usually based on the widely accepted biopsychosocial approach; it is recommended as a second-line treatment for patients with CLBP. However, the optimal dose, content or delivery of such a multidisciplinary rehabilitation programme is unknown. Against this backdrop, a new multidisciplinary rehabilitation programme, named *the integrated programme* was developed, feasibility-tested and evaluated in a randomised controlled trial (RCT).

2. The integrated programme

The development, feasibility-testing and evaluation of the integrated programme was based on the Medical Research Council's (MRC) guidance on developing and evaluating complex interventions (32, 36). The MRC's guidance was used as the underlying methodological framework as it offered a systematic four-stage model to structure the research process. Figure 1 illustrates the model comprising four stages, and 12 related elements (32). The process is seen as dynamic and iterative rather than linear or cyclical (32).

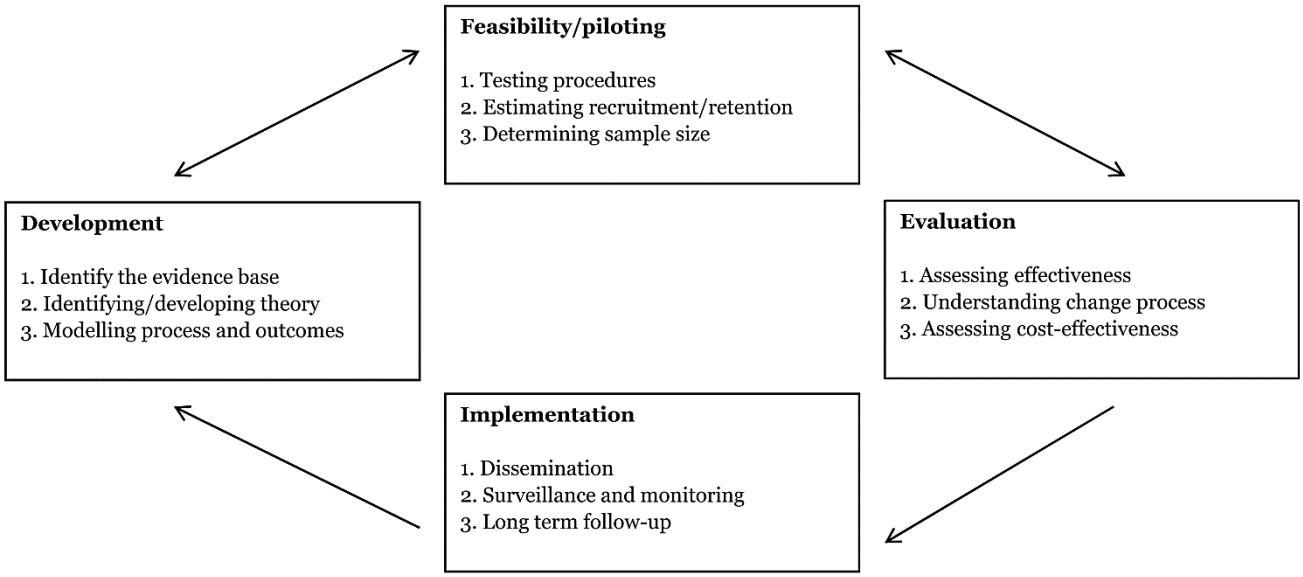


Figure 1. The Medical Research Council's four-stage model with the 12 related elements (32). Reproduced with permission of the UK Medical Research Council (Appendix 4).

In the first part of this chapter, the MRC's guidance (32, 36) in combination with inspiration from Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline (CReDECI 2) (37) was used to structure and ensure comprehensive reporting. In the last part of this chapter, the Patient and Public Involvement (PPI) process was reported with inspiration from Guidance for Reporting Involvement of Patients and the Public 2 short form (GRIPP2) (38).

2.1 The MRC's guidance applied to the research process

To improve the transparency and create an overview, the methods used at each of the four stages and the 12 related elements following the MRC's guidance (32, 36) are outlined in Table 1. The results of this research process are presented subsequently and follow the same structure.

Table 1. Overview of methods used in the research process according to the four stages and the 12 related elements described in the Medical Research Council's guidance (32, 36).

Stage	Elements	Methods
Development	Identifying the evidence base	A systematic approach was used to identify a Cochrane systematic review and meta-analysis (7). An updated literature search in CENTRAL, Medline, Embase, PsycINFO and CINAHL was performed in February 2016. Clearly ineligible trials were excluded based on title and abstract, and the remaining trials were reviewed in full text. The updated literature search and assessment were identical to criteria used in the Cochrane review (7).
	Identifying/developing theory	When conducting an RCT within the field of CLBP and rehabilitation, the biopsychosocial approach was considered essential. The Chronic Care Model was identified from discussions with other researchers.
	Modelling processes and outcomes	A six-step modelling scenario consisted of the following steps (39): Step 1 Installing a project team and formulating the key objectives: meetings. Step 2 Getting consensus on the components: meetings with patients and stakeholders (includes providers, administrative and management staff). Step 3 Clustering of clinical activities into key components and building a process flow: meetings with providers and management staff. Step 4 Organising the process and allocating resources: meetings with administrative and management staff. Step 5 Describing key interventions: existing descriptions were updated by providers and the project team. Step 6 Translation into a set of process and outcome indicators: literature, focus groups with patients using a semi-structured interview guide, and providers voting for their two favourite outcomes. The final decision about the outcomes was taken by the PhD candidate. The outcome measures were primarily chosen on the basis of the literature. Three providers with different backgrounds chose their preferred psychological outcome measure amongst Pain Self-Efficacy Questionnaire, Fear Avoidance Questionnaire and Pain Catastrophising Scale.

Stage	Elements	Methods
Feasibility/ Piloting	Testing procedures	Opinions about whether the integrated programme was appropriate, feasible and acceptable were gained from meetings and focus groups using a semi-structured interview guide with former patients in the existing programme, an internal pilot group (n = 3) (40), and stakeholders. Two patients were involved in the development of the participant information and informed consent form. Two patients tested the database set-up in terms of time consumption and layout.
	Estimating recruitment/ retention	Patient flow, recruitment strategy and duration of inclusion were discussed at meetings with administrative and management staff. Focus groups with patients using a semi-structured interview guide were used to learn about barriers to recruitment, and the proportion of eligible patients willing to participate.
	Determining sample size	Sample size was calculated based on the literature and a feasibility-test including 12 patients completing the Oswestry Disability Index when they started and ended the existing programme (Chapter 4).
Evaluation	Assessing effectiveness	The design was chosen based on meetings involving members of the project team and recommendations from a statistician.
	Understanding change process	No exact recipe on how to perform a process evaluation exists (41-43), but it is recommended to: 1) plan, 2) design and conduct, 3) analyse, and 4) report (41, 42). Background, purpose and methods applied will be presented in Section 2.1.3.2 as more elaboration was needed regarding the process evaluation.
	Assessing cost-effectiveness	This was outside the scope of this dissertation.
Implementation	Dissemination	Publication/submission of three peer-reviewed papers. Presentations at national and international meetings and conferences. Results from the process evaluation and the evaluation of the RCT were fed back to stakeholders at meetings. Patients included in the RCT will be emailed the results in layman language formulated in cooperation with a patient representative.
	Surveillance and monitoring	Design of a database and obtained informed consent allowing for 12-month follow up served the purpose of surveillance, monitoring and long-term follow up with the possibility of prolongation
	Long-term follow-up	

2.1.1 Development

2.1.1.1 Identifying the evidence base

A Cochrane systematic review and meta-analysis on multidisciplinary biopsychosocial rehabilitation for CLBP (7) together with two additional RCTs (44, 45) were identified (Figure 2).

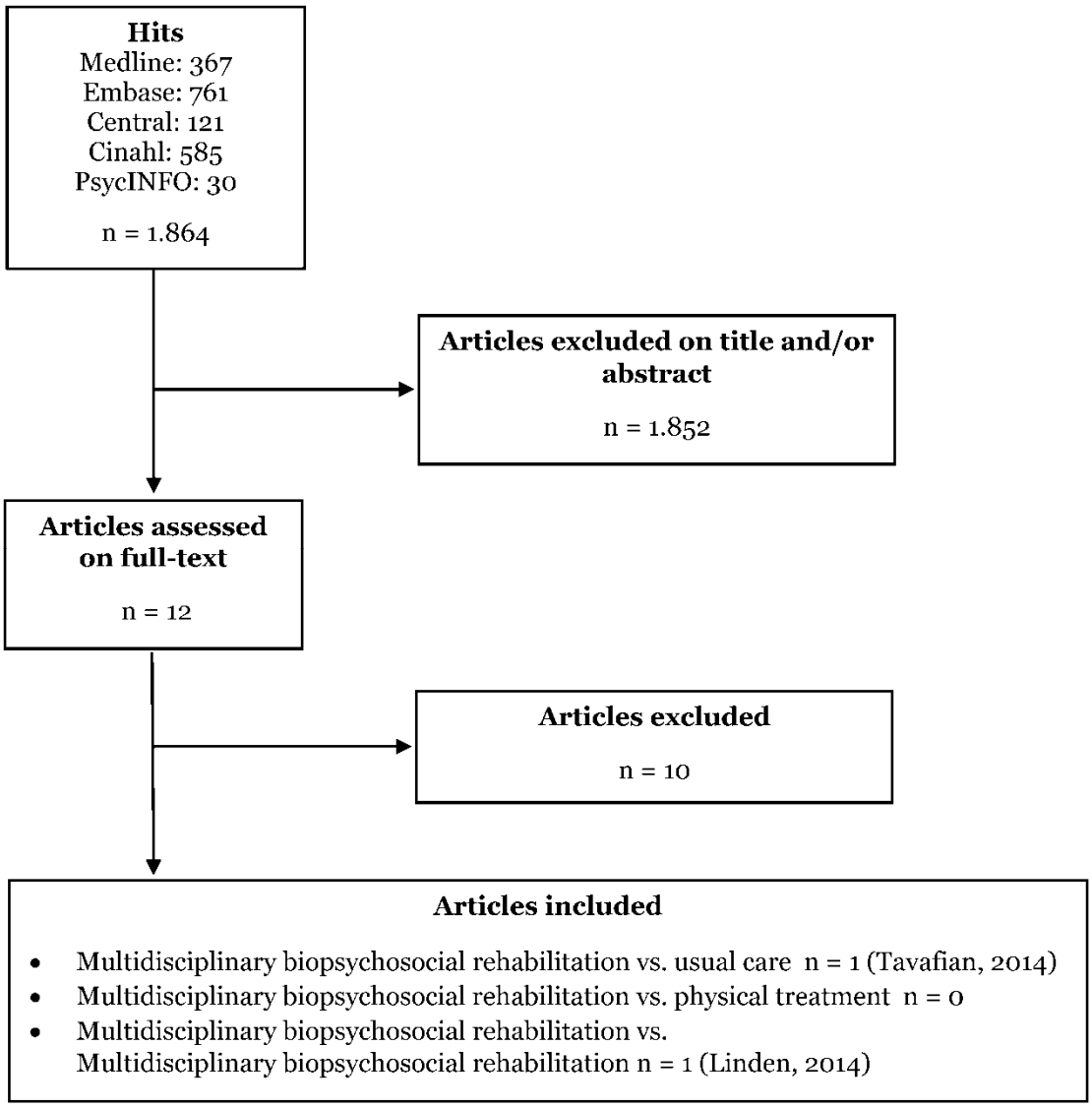


Figure 2. Flow-chart illustrating the updated literature search and assessment in February 2016.

In total, 13 specific RCTs comparing two or more rehabilitation programmes were of notable interest in the development process and formed the evidence base for the integrated programme; 12 RCTs were identified in the Cochrane review (7) and one additional RCT (44) from the updated literature search. In brief, the 13 RCTs were very heterogenous as they compared a variety of inpatient- and outpatient programmes, using diverse clinical activities, different provider compositions, various follow-up lengths, and different outcome domains and outcome measures (7, 44). Four of the RCTs had disability as the primary outcome (46-49) (Table 2).

Of the 13 RCTs, only one RCT assessed the effect of adding booster sessions (seven phone calls) to a 4-week multidisciplinary inpatient rehabilitation programme, aiming to demonstrate if adding the booster sessions had additional benefit in stabilising treatment successes one year after discharge (48). The RCT found a slight, but not statistically significant, advantage of adding the booster sessions compared with a 4-week multidisciplinary inpatient rehabilitation programme without booster sessions (48) (Table 2).

None of the 13 RCTs explicitly claimed to assess integration of knowledge, skills and behaviours from an inpatient stay into the daily life of the patients.

Table 2. Overview of the four RCTs comparing two or more rehabilitation programmes having disability as the primary outcome.

Author [Year] (Ref.)	Number of participants (in groups)	Intervention 1	Intervention 2	Intervention 3	Outcome domains (outcome measurements)	Follow up	Conclusion in terms of disability
Abbasi [2012] (46)	36 (12/12/12)	Standard medical care -> continuation of routine treatment based on ordinary medical care.	P-MPMP -> Conventional patient-oriented multidisciplinary pain management programme. 7x weekly sessions of 2 hours (6/group) + session with doctor + session with physiotherapist Light mobilisation, coping skills training, education regarding anatomy, physiology, medication, exercise session. Outpatient	SA-MPMP -> As P-MPMP + involvement of spouse	Primary: - Disability (Roland and Morris Disability Questionnaire) - Pain severity (Visual Analogue Scale) Secondary: - Fear avoidance (Tampa Scale of Kinesiophobia) - Pain catastrophizing (Pain Catastrophizing Scale) - Psychological distress (Depression, Anxiety and Stress Scale) - Marital adjustment (Marital Adjustment Test)	12 months	No significant between-group differences were found for Roland and Morris Disability Questionnaire scores.

Author [Year] (Ref.)	Number of participants (in groups)	Intervention 1	Intervention 2	Intervention 3	Outcome domains (outcome measurements)	Follow up	Conclusion in terms of disability
Leeuw [2008] (47)	85 (42/43)	Exposure in vivo treatment (EXP). 16x 1hr sessions, 2/week. Information about diagnosis, imaging, continued active approach, treatment rationale. Establishment of hierarchy of feared activities, explanation of fear avoidance model, gradual, systematic exposure to feared activities. Behavioral experiments to test consequences of engagement in feared activities.	Graded Activity (GA). 26x 1hr sessions, 2/week. Information about diagnosis, imaging, continued active approach, treatment rationale. Identification of functional treatment goals, quota-based gradual increase in performance of functional activities. Two sessions included spouses.		Primary: - Disability (Quebec Back Pain Disability Scale) - Main complaints (Patient Specific Complaints) Secondary: - Harmfulness of activities (Photograph Series of Daily Activities) - Pain catastrophizing (Pain Catastrophizing Scale) - Daily activity (accelerometer) - Pain intensity (McGill Pain Questionnaire)	6 months	No significant difference was found between treatment conditions in functional disability.

Author [Year] (Ref.)	Number of participants (in groups)	Intervention 1	Intervention 2	Intervention 3	Outcome domains (outcome measurements)	Follow up	Conclusion in terms of disability
Mangles [2009] (48)	363 (131/113/119)	Traditional Orthopedic Rehabilitation treatment. 3 weeks of individual sessions or open groups (inpatient) Mostly physical/orthopedic treatment including active physiotherapy, passive modalities and occupational therapy.	Behavioral-medical Rehabilitation Treatment. 4-week inpatient stay in groups of 10-12 patients. Treatment as in the Traditional Orthopedic Rehabilitation treatment + implementation of explicit psychologic treatment elements. - Group session of psychologic pain management (9 sessions of 90 minutes) conducted by behavioral psychotherapist. - Home assignments - Progressive muscle relaxation group	Behavioral-medical Rehabilitation Treatment **plus** subsequent booster sessions. 4-week inpatient stay in groups of 10-12 patients. Treatment as in Behavioral-medical Rehabilitation Treatment + booster sessions consisting of 7 telephone calls of 20 minutes over 12 weeks to reinforce inpatient topics, problem-solving, goal setting, relaxation, coping etc.; ending with home-work. Handouts were given on all topics before beginning this aftercare treatment.	- Disability (Pain Disability Index) - Depression (Beck Depression Inventory) - Pain perception (The Pain Perception Scale) - Health-status (SF-12 Health Survey) - Coping (German Pain Management Questionnaire) - Pain Self-efficacy (Pain Self-Efficacy Questionnaire) - Life satisfaction concerning health (German Life Satisfaction Questionnaire) Not stated which was primary.	12 months	No treatment effect in terms of disability. Only slightly advantages for the subsequent booster sessions were found.

Author [Year] (Ref.)	Number of participants (in groups)	Intervention 1	Intervention 2	Intervention 3	Outcome domains (outcome measurements)	Follow up	Conclusion in terms of disability
			- Opportunity to engage in weekly individual sessions with psychotherapist	Phone calls were conducted by clinical psychologist.			
Smeets [2008] (49)	223 (58/53/61 and waiting list controls=51)	Graded activity with problem solving training (GAP) 3 group sessions + max 17 individual sessions of 30 minutes), problem-solving (10 group sessions x 90 min), modification of dysfunctional beliefs, HEP increasing activity.	Active physical treatment (APT) 10 weeks. 3x/week 1 hour and 45 minutes of aerobic training, strength and endurance.	Combination of GAP + APT APT three/week and GAP once/week Frequency and duration as in APT and GAP.	Primary: - Disability (Roland and Morris Disability Questionnaire) Secondary: - Pain (Visual Analogue Scale and McGill) - Patients main complaints - Self-perceived improvement - Depression (Beck Depression Inventory) - Six physical performance tests	6 months 12 months	The combination treatment is no better treatment option.

2.1.1.2 Identifying/developing theory

No single theory of rehabilitation exists (50), but based on the knowledge presented in Chapter 1, the biopsychosocial approach (15, 16, 18-20) was the dominant theory. In addition, the Chronic Care Model (51-53) was considered appropriate. Together, the two approaches formed the theoretical foundation of the integrated programme.

The biopsychosocial approach has been explained, discussed, and interpreted during the past 40 years. Two interpretations of the biopsychosocial approach were used to underpin the integrated programme, namely the ICF model (16) and four editorials arguing for a new rehabilitation approach (15, 18-20).

The ICF model embraces the biopsychosocial dimensions of disability by viewing functioning and disability, and contextual factors relevant to a given health condition (16). The ICF model offers a framework for applying the biopsychosocial approach into clinical practice (6) especially into rehabilitation where the consequences of disability are managed (6, 15, 17, 27, 30, 54). In the LBP field, it has been suggested that the ICF model can serve as the foundational underpinning of a comprehensive framework to better guide rehabilitation of patients with LBP (55). The ICF model is an important element in any proposed theory of rehabilitation, and a valuable framework from which to begin any programme of rehabilitation, although it cannot stand alone (56).

The four editorials enhanced the following elements as sound, logical and/or evidence-based in rehabilitation (15, 18-20):

- Rehabilitation works in the context of a complex system (18).
- The patient must be actively engaged and practise activities as much as possible in the fundamental process of learning (15, 18). In terms of learning, there are some important principles: 1) the patient must want to learn, 2) the patient must practise, 3) the patient needs feedback on his/her performance, 4) the patient needs to take responsibility for his/her learning, and 5) practice should be in the context where the activity is to be undertaken normally (15). Face-to-face therapy is an important, but not dominant, component in rehabilitation (18). Of great importance is the amount of time the patient spends learning (20).
- A skilled multidisciplinary rehabilitation team is required to effectively manage the complex problems seen in rehabilitation (18-20). The goal is to teach the patient knowledge, skills and self-management, and arrange the context in an optimal way (19, 20).

The abovementioned elements correspond with elements recommended in the rehabilitation of patients with LBP (6).

Moreover, some of the elements have also been described in the Chronic Care Model (51-53). In the Chronic Care Model, evidence of effective changes needed to improve chronic care has been synthesised (51-53). At the center of the Chronic Care Model is a productive interaction between an informed, actively engaged patient and a prepared, proactive practice team united in a collaborative relationship (52, 53). The role of the practice team is to ensure that patients are equipped with the requisite confidence and skills to self-manage their health condition (51-53). This can be supported by using regular follow-up interactions (hereafter termed "booster sessions") (51-53). Furthermore, due to the time horizon and fluctuating course of chronic health conditions, regular interactions between the patient and the practice team are essential. Booster sessions can take the form of practice-initiated follow-up visits, but methods other than face-to-face contacts can be used (e.g. telephone calls). Regardless of the form of contact, the purpose of the booster sessions is to evaluate response to therapy and self-management competences, and to adjust treatment (51, 53).

Collectively, the chosen theories underpinned the justification of the integrated programme. The integrated programme targeted the biopsychosocial factors driving disability, and further, it acknowledged the influence of the context. With the integrated programme, the delivery of an existing rehabilitation programme was changed by alternating inpatient stays (including booster sessions) and home-based activities. During the inpatient stays, patients were motivated, assisted and challenged by a multidisciplinary team in the process of learning. During the home-based periods, the patients were encouraged to integrate their newly obtained knowledge, skills and behaviours into their daily life. The booster sessions further allowed for adjustment and modification of the rehabilitation plan.

2.1.1.3 Modelling process and outcomes

Step 1

A project team comprising the PhD candidate, supervisors and management staff was established. It was decided to name the new rehabilitation programme "the integrated programme", since the main feature was to enhance integration of knowledge, skills, and behaviours from inpatient stays into the patients' daily life.

Step 2

The overall aim of the RCT was to compare two different ways of delivering a rehabilitation programme, thus, it was decided to include exactly the same clinical activities in the integrated programme and the comparator being the existing programme. The clinical activities in the existing programme were originally based on the literature and knowledge about CLBP using the biopsychosocial approach.

During the consensus process on how to deliver the integrated programme, the providers argued for the booster sessions and the prolonged rehabilitation time as it would give the patients the opportunity to integrate knowledge, skills and behaviours into their daily life while still being in contact with the providers. Most patients were positive about the alternation between inpatient stays and home-based activities.

The organisational impact of the integrated programme was assessed, and it was deemed possible to conduct the proposed RCT in the setting under study.

Step 3

The clinical activities were grouped into 10 key components delivered by the providers (Table 3). Together, the 38 clinical activities targeted biophysical, psychological, social, and lifestyle factors.

Table 3. Key components and the related 38 clinical activities in the rehabilitation programmes (57).

Key component	Clinical activity
Clinical assessment	Physical assessment Psychosocial assessment
Motivation and change	Instruction in exercise app Introduction to rehabilitation Exercise theory Introduction to mindfulness Involvement of relatives Motivation and anchoring The next step
Pain knowledge and management	Chronic pain and chronic back pain Experiences with pain Knowledge about pain Knowledge about analgaesic medicine Living with pain
Multidisciplinary intervention	Welcome meeting Multidisciplinary conference Open counselling Midterm evaluation
Exercise and physical activity	Aqua gymnastics Circuit training Intro electric bicycle Exercise capacity training Healthy feet Closing activity
Individual counselling	Individual nurse counselling (focusing on psychologic aspects) Individual physiotherapy counselling Individual occupational therapy counselling Individual dietary counselling Individual rheumatologic counselling
Essential activity	Activity and health Balanced activity Activity and social relations Lifelong activity
Activities of daily living	Sleep House and garden
Nutrition and weight loss	Permanent weight loss strategies Healthy lifestyle
Individual exercise	Individual exercise

Step 4

Tasks and roles of providers and administrative staff were described in internal documents and in a trial flow illustrating the patients' trajectory through the inclusion process.

Step 5
A detailed description of the integrated programme following the Template for Intervention Description and Replication (TIDieR) checklist (58) was undertaken and published (57).

Step 6
The primary and secondary outcomes and outcome measures were chosen (Section 4.2.5).

2.1.2 Feasibility/piloting

2.1.2.1 Testing procedures
The main changes and initiatives were:

1) Fine-tuning of administrative procedures (e.g. revision of the welcome letter, nominating persons responsible for phone calls and data collection, and documentation of informed consent form in the electronic health records).

2) Overbooking of two to three patients in each group due to patient-initiated postponements.

3) Arranging a place to rest on the pre-admission day and at the 6-month follow-up visit, and assigning all groups a specific dinner table.

4) Adjusting layout and minor features in the database.

2.1.2.2 Estimating recruitment/retention
The number of eligible patients and the intended willingness to participate were considered large enough to recruit a sufficient number of patients.

2.1.2.3 Determining sample size
Sample size was calculated (Section 4.2.7.1).

2.1.3 Evaluation

2.1.3.1 Assessing effectiveness
A single-centre, pragmatic, two-arm parallel RCT was chosen as an appropriate design. The RCT is further described in Chapter 4.

2.1.3.2 Understanding change processes

As advocated when working with complex interventions, a process evaluation was nested into the RCT (32). A process evaluation is useful when interpreting the results to explain discrepancies between expected and observed outcomes, or when clarifying why and how a successful intervention works (36, 43, 59). In brief, an RCT assesses if an intervention is working or not, while a process evaluation seeks to understand why the intervention is working or not (41, 43, 59).

The process evaluation relied on a framework that consisted of the following three key components:

1) understand how a complex intervention is implemented,
2) clarify mechanisms of impact, and
3) identify interaction with the context

(41, 42, 60).

The three key components, the related subdivision and a corresponding explanation is provided in Table 4.

Table 4. Key components, subdivision and corresponding explanation of a process evaluation. Inspired by and combined from relevant articles (41, 42, 60).

Key components	**Subdivision**	**Explanation**
Implementation - what is implemented and how? The extend to which the intervention has been implemented and received by the intended participants.	Implementation process.	How delivery is achieved; training, resources etc.
	What is delivered: 1) Fidelity 2) Dose 3) Adaptations 4) Reach	 1) The extent to which the intervention was delivered as intended. 2) The quantity of intervention implemented. 3) Adaptations often arise when the intervention is implemented across different contexts. 4) Whether the intended participants come into contact with the intervention, and how.
Mechanisms of impact – how does the delivered intervention produce change? When capturing mechanisms of impact, participants' response to, and interaction with, the intervention, as well as unexpected pathways and consequences can be described.	Participant response to and interactions with, the intervention.	The mechanisms through which interventions bring about change.
	Mediators.	
	Unexpected pathways and consequences.	
Context - how does context affect implementation and outcomes? When focusing on context, focus can be on how context shapes implementation and influences whether intervention mechanisms work.	Contextual factors that shape theories of how the intervention works.	Anything external to the intervention that may act as a barrier or facilitator to its implementation, or its effect.
	Contextual factors that affect (and may be affected by) implementation, intervention mechanisms and outcomes.	
	Causal mechanisms present with the context which act to sustain the status quo, or potential effects.	

In the following the methods used to 1) plan, 2) design and conduct, 3) analyse, and 4) report (41, 42) the process evaluation will be elaborated.

Firstly, the plan was pre-specified, and all issues known to potentially affect the results were discussed. The purpose of the process evaluation was to shed light on selected aspects of implementation, mechanisms of impact and context related to the integrated programme in order to seek to understand and explain the results of the RCT.

Secondly, to underpin the design and conduct, a logic model was developed and refined until it depicted the integrated programme including justification, planned work and intended results (61). A pictorial representation can be seen in Figure 3. Logic models seeks to illuminate the chosen theories, is a map of the road ahead (61), and may reveal possible interactions (62) making it useful when identifying relevant process research questions (41). Thus, the logic model is a simplification of a complex reality, and is useful across all the stages of the research process.

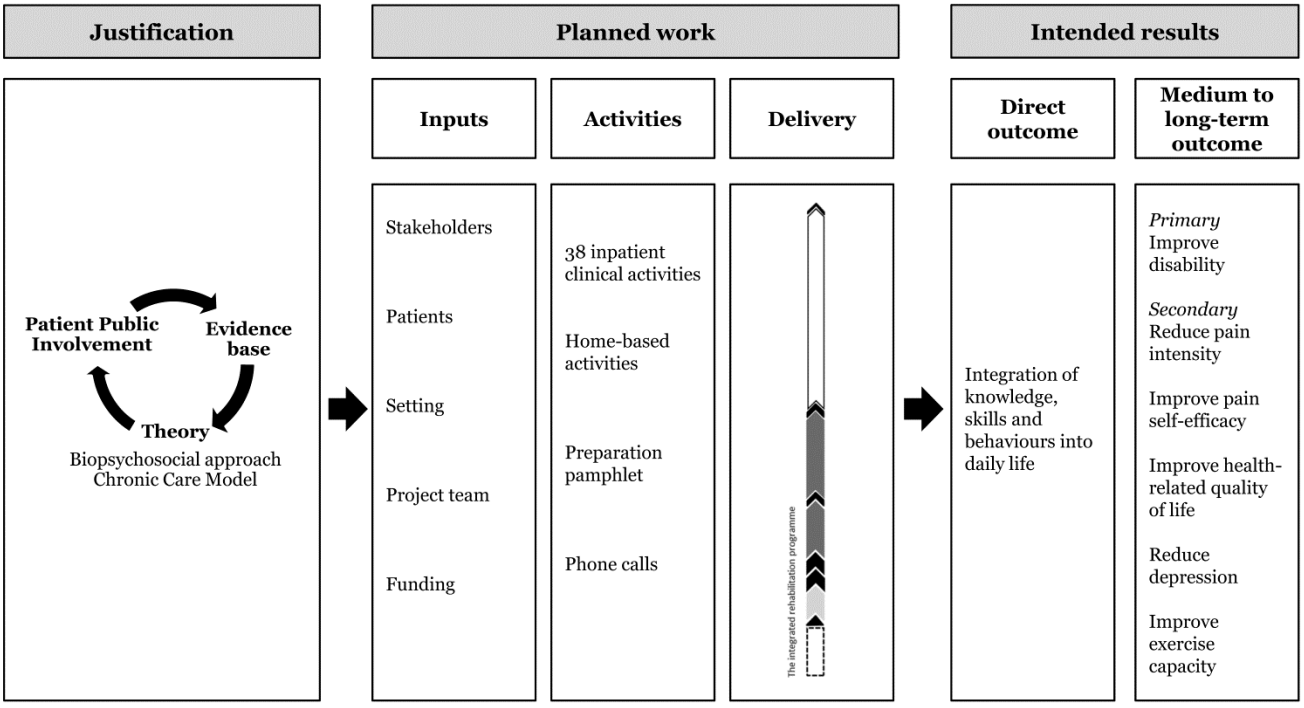


Figure 3. Logic model of the integrated programme.

Process research questions 1-5 were identified prior to the RCT (Figure 4). The process evaluation was designed with flexibility, as complex interventions are inherently unpredictable (41, 42), thus, research question 6 occurred during the evaluation of the RCT (Figure 4). A combination of

qualitative (process research questions 1-4) and quantitative methods (process research questions 5-6) were used.

The PhD candidate analysed the process research questions, except for process research questions 3 and 4, which were analysed in-depth by two Masters students (data not published).

The PhD candidate provided ongoing verbal and written feedback at meetings or via email on process findings to stakeholders (includes providers, administrative and management staff), thereby striving for quality improvement (61).

Thirdly, the analyses of the qualitative process findings (process research questions 1-4) were performed before the statistical analyses. Quantitative data (process research questions 5-6) on adherence and waiting time were used in secondary analyses.

Fourthly and lastly, findings were reported systematically and explicitly in line with recommendations for process evaluations (41-43). The findings from process research questions 1-4 were briefly summarised (Section 5.5), and the findings from process research questions 5 and 6 were reported in Studies 2 and 3 (Sections 5.3 and 5.4).

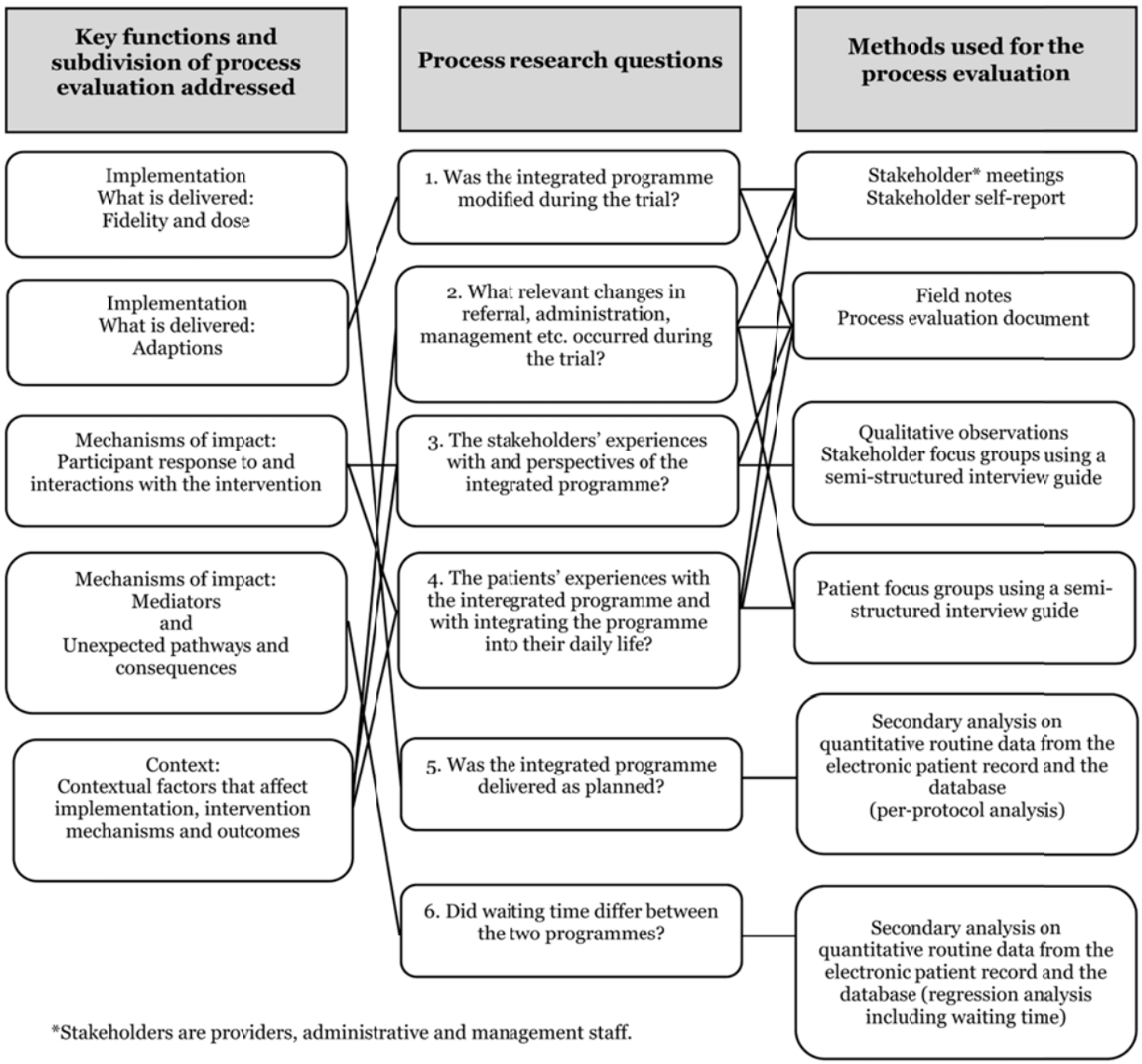


Figure 4. The three key functions and subdivisions of process evaluation addressed (column 1), process research questions (column 2) and methods used for the process evaluation (column 3) (63).

2.1.3.3 Assessing cost-effectiveness

This was outside the scope of this dissertation.

2.1.4 Implementation

Implementation in clinical practice was outside the scope of this dissertation. However, in line with recommendations (32), implementation was considered and discussed with stakeholders early in the research process as there was no need to develop and evaluate a rehabilitation programme that was unlikely to be implemented following the evaluation.

2.2 Patient and public involvement

Patient and Public Involvement (PPI) is defined as research being carried out with or by members of the public rather than to, about, or for them (64). The interest in PPI is growing (38, 65), and in rheumatology, the European League Against Rheumatism has published eight recommendations for the inclusion of patients in research (66). Although sparsely described in the MRC's guidance (32, 36), PPI was prioritised as a part of this research process since preferences and concerns might differ between researchers, patients, and stakeholders (64-66).

In the current research process the purpose of PPI was to consult and collaborate with patients and stakeholders as research partners in the development, feasibility-testing and evaluation of the RCT.

The patients recruited for the PPI process were randomly selected among those who were inpatients at different time points relevant to the research project. Thus, they represented a diversity of patients who could contribute with a variety of different reflections and personal experiences with CLBP and related disability. Furthermore, it minimised the logistical challenge of gathering the same group of patients repeatedly. All patients who participated in the PPI process volunteered. The stakeholders involved had experiences with delivering rehabilitation in the setting under study. Data obtained from meetings and focus groups were stored in meeting summaries, the PhD candidate's field notes and a process evaluation document. PPI in this research project did require time resources, but no direct costs.

A completed GRIPP2 short form reporting PPI in the research process can be found in Appendix 5.

3. Aims

The overall aim of this dissertation was to contribute new knowledge about the delivery of multidisciplinary rehabilitation programmes to patients with CLBP. For this purpose, the integrated programme was developed, feasibility-tested and evaluated.

The three specific aims listed below correspond to the three studies undertaken:

Aim 1 (Study 1)

To justify and describe the integrated programme in detail prior to an RCT.

Aim 2 (Study 2)

To compare the effectiveness of the integrated programme with the existing programme in terms of back-specific disability in patients with chronic low back pain at the 6-month follow up.

It was hypothesised, that the integrated programme would be superior to the existing programme.

Aim 3 (Study 3)

To compare the effectiveness of the integrated programme with the existing programme in terms of back-specific disability in patients with chronic low back pain at 12-month follow up.

It was hypothesised, that the integrated programme would be superior to the existing programme.

4. Methods

Study 1 is a justification and detailed description of the integrated programme. The evaluation of the RCT is reported in Study 2 (6-month follow up) and Study 3 (12-month follow up). Table 5 presents an overview of the three studies included in this dissertation. Following the overview, the methods used are presented in further detail; Study 1 on its own, and Studies 2 and 3 together as they were closely related.

Table 5. Overview of design, applied reporting guidelines, outcome domains and outcome measures, follow up and primary statistical analyses.

Study	Design	Reporting guidelines	Outcome domains (outcome measures)	Follow up	Primary statistical analyses
1	Descriptive study	TIDieR (58) CERT (67)	-	-	-
2	RCT	CONSORT 2010 (68) CONSORT extensions (69-71) GRIPP2 short form (38)	Primary: Disability (ODI) Secondary: Pain intensity (NRS) Pain self-efficacy (PSEQ) Health-related quality of life (EQ-5D 5L) Depression (MDI) Physical activity (Three questions) Exercise capacity (Aastrand test)	6-month	Complete case analysis. Multiple linear regression using change score as the dependent variable, rehabilitation programme as the independent variable, and the corresponding baseline score as covariate.
3	RCT	CONSORT 2010 (68) CONSORT extensions (69-71) GRIPP2 short form (38)	Primary: Disability (ODI) Secondary: Pain intensity (NRS) Pain self-efficacy (PSEQ) Health-related quality of life (EQ-5D 5L) Depression (MDI) Physical activity (Three questions) Exercise capacity (Aastrand test)	12-month	Intention-to-treat analysis including the four similar measurement time points. Difference in change between the two groups (integrated programme minus existing programme) from baseline to 12-month using a linear mixed model with a random intercept including time, group and the interaction between group and time as the explanatory variables.

TIDieR: Template for Intervention Description and Replication; CERT: Consensus on Exercise Reporting Template; CONSORT: Consolidated Standards of Reporting Trials; GRIPP2 short form: Guidance for Reporting Involvement of Patients and the Public 2 short form; ODI: Oswestry Disability Index; NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; EQ-5D 5L: EuroQol-5 Domain 5-level; MDI: Major Depression Inventory

4.1 Study 1

Structure and detail was provided primarily using the TIDieR checklist (58) of which the 12 items are listed and explained in Table 6.

Table 6. Items and item categories of the TIDieR checklist along with a brief item description (58).

Item	Item category	Brief item description
1	Brief name	Provide the name or a phrase that describes the intervention
2	Why	Describe any rationale, theory, or goal of the elements essential to the intervention
3	What (materials)	Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (for example, online appendix, URL)
4	What (procedures)	Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.
5	Who provided	For each category of intervention provider (for example, psychologist, nursing assistant), describe their expertise, background and any specific training given.
6	How	Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.
7	Where	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.
8	When and how much	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.
9	Tailoring	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.
10	Modifications	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).
11	How well (planned)	If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.
12	How well (actual)	If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.

For the purpose of clarity, the 38 different clinical activities included in the integrated programme were each presented in an activity sheet combining “What (procedures)”, “Tailoring”, “Who provided”, “How” and “When (and how much)” from the TIDieR checklist (58). In addition, the Consensus on Exercise Reporting Template (CERT) checklist (67) was used to ensure proper reporting of the exercise interventions, highlighting the importance of including specific information about e.g. frequency, duration, intensity and supervision.

Thus, the two checklists (58, 67) were used to achieve transparent and complete description of the 38 clinical activities. An example of a completed activity sheet is presented in Table 9.

4.2 Studies 2 and 3

4.2.1 Choice of design and its explanation

These two studies occurred in the context of a single-centre, pragmatic, two-arm parallel, RCT (63, 72).

When developing the RCT, we aimed for a high degree of applicability, meaning that the results of the RCT were intended to have the ability to directly inform, and be relatively easy to apply to, clinical practice (73, 74). Aiming to maximise applicability corresponds to conducting a pragmatic trial (73). While a pragmatic trial is designed to determine intervention effects under usual conditions, an explanatory trial is designed to determine intervention effects under ideal circumstances (73, 75). The difference between the two approaches is not dichotomous rather a continuum (73, 74). PRECIS-2 (second version of Pragmatic Explanatory Continuum Indicator Summary) is a tool developed for use when designing the trial; it aims to help the researcher to make the purpose explicit and ensure that design choices and purpose are concordant, and further, to make the researcher aware of the trial's location on the pragmatic-explanatory continuum (73).

In the development of the RCT, we were not aware of PRECIS-2 (73), and hence the tool was used retrospectively in order to reveal the (actual) position of the RCT on the pragmatic-explanatory continuum. The PhD candidate and the main supervisor assessed each domain individually. After that, a discussion followed and consensus was obtained.

The PRESIC-2 assessment was performed following four steps (73):

Step 1. What design approach are you taking? (Section 4.2.1)

Step 2. Consider your trial design choices for each of the nine PRECIS-2 domains (Table 7).

Step 3. Score 1 to 5 for the choices made in step 2 and/or mark on the PRECIS-2 wheel (score 1 is "very explanatory", score 2 is "rather explanatory", score 3 is "equally pragmatic and explanatory", score 4 is "rather pragmatic", and score 5 is "very pragmatic") (Table 7 and Figure 5).

Step 4. Review the PRECIS-2 wheel (Figure 5).

Table 7. Overview of domains, rationale for design choices and the corresponding score given by applying PRECIS-2 to this RCT.

	Domain	Rational for design choices	Score
1	Eligibility	The eligibility criteria were very much identical to those in the usual setting – except for exclusion of patients with axial spondyloarthritis and Oswestry Disability Index score <21 (Section 4.2.2).	4
2	Recruitment	Patients referred to the usual setting were recruited without knowledge of the RCT. No extra effort was made to enhance referral to the usual setting.	5
3	Setting	Full accordance between the setting of the RCT and the setting where the results are likely to be applied.	5
4	Organisation	The integrated programme drew upon existing competences among providers and administrative staff.	3
5	Flexibility (delivery)	The integrated programme was partially tailored to ensure a degree of person-centeredness. There was no strict protocol in terms of the content and no restrictions of co-interventions.	5
6	Flexibility (adherence)	Adherence to inpatient days was recorded, but patients were not excluded based on this record and no effort was made to improve adherence to inpatient days. Adherence to home-based activities was not measured.	5
7	Follow-up	Identical follow up in both rehabilitation programmes (6-month and 12-month), but slightly more data collection in the integrated programme.	4
8	Primary outcome	Choice based on the literature and PPI confirming that the primary outcome was meaningful to patients and providers.	5
9	Primary analysis	A complete case analysis only including data from completers (Study 2).	1
		An intention-to-treat analysis using all available data regardless of adherence and/or complete follow-up data (Study 3).	5

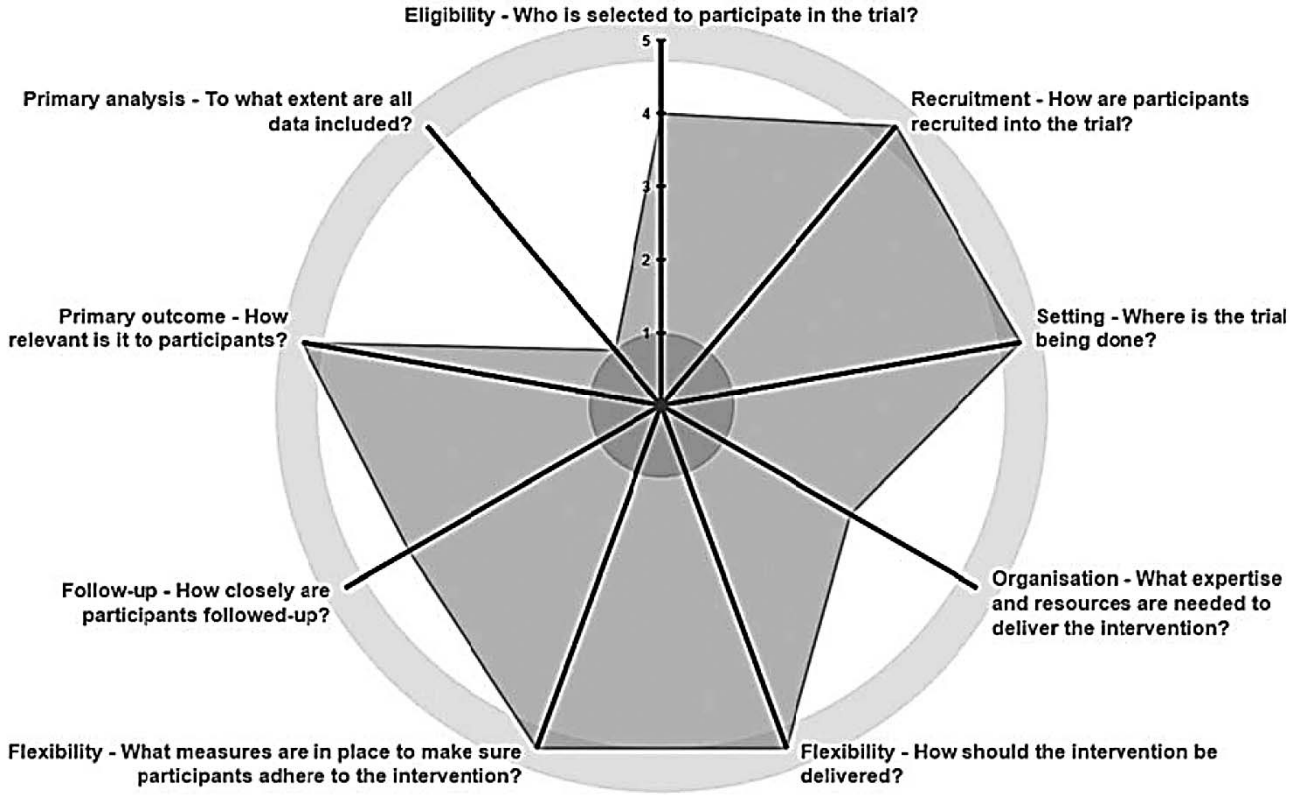


Figure 5. The PRECIS-2 wheel depicting Study 2 (76).

4.2.2 Setting and participants

The setting under study was a multidisciplinary rehabilitation centre, owned and operated by the Danish Rheumatism Association. Patients with rheumatic and musculoskeletal diseases were referred from general practitioners or hospital departments to a tax-funded rehabilitation programme. Allowing for approximately 28 patients to be inpatients from Monday to Friday, a running schedule starting a group of six to eight patients on a rehabilitation programme each week meant that there were constantly four groups of patients at the rehabilitation centre at the same time.

Patients were included in the RCT if they had had CLBP for more than 12 months (+/- sciatica and/or widespread pain) and if they were 18 years or older. The RCT exclusion criteria were: 1) severe systemic diseases (American Society of Anesthesiologists Physical Status classification system > 3 (77)), 2) a diagnosis of axial spondyloarthritis, 3) spinal fracture within the last three 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 (ODI) score < 21 (78)).

The rheumatologist at the rehabilitation centre identified potentially eligible patients based on the referral request and a list of ICD-10 diagnosis codes. Before inclusion, a research assistant performed eligibility checks by telephoning potentially eligible patients. Participant information and an informed consent form were emailed by the research assistant, and if a signed version was returned, the patient was included. The final eligibility check was performed by the rheumatologist on the first inpatient day.

4.2.3 Randomisation and blinding

A secure electronic database was used to email questionnaires, store data, and generate the random allocation sequence. A computer-generated randomisation with 1:1 allocation in random blocks of six ensuring allocation concealment (79) was performed by the research assistant. Randomisation was stratified on the basis of baseline disability (ODI score over/under 41) (78) to achieve approximate balance in mean disability levels (79). The research assistant informed patients about intervention allocation and appointed dates for the allocated rehabilitation programme. The patients had wait time until the next available rehabilitation programme, as this was usual practice at the rehabilitation centre.

Blinding of patients and providers was not possible due to the nature of the rehabilitation programmes (31, 79), although attempts were made to blind patients to the hypothesis by informing them that the RCT aimed to compare two rehabilitation programmes both which met current recommendations. This was done in order to equalise expectations for the allocated rehabilitation programme (31, 79). The physiotherapists were blinded to the result of the baseline exercise capacity test when performing the 6-month follow-up exercise capacity test. The PhD candidate performed the statistical analyses and was blinded to allocation.

4.2.4 Interventions

The key difference between the two rehabilitation programmes was how they were delivered (Figure 6).

Patients in *the integrated programme* participated in: 1) a pre-admission day, 2) two weeks of home-based activities, 3) a two-week inpatient stay (nine days excluding the weekend), 4) four weeks of home-based activities, 5) an initial two-day inpatient booster session, 6) six weeks of home-based activities, 7) a second two-day inpatient booster session, and 8) a 6-month follow-up visit. In total, the integrated programme comprised 15 inpatient days.

Patients in *the existing programme* participated in: 1) a four-week inpatient stay (20 days excluding the weekends), and 2) a 6-month follow-up visit, resulting in 21 inpatient days. The existing programme has been usual practice for more than 15 years.

Differences and similarities between the two rehabilitation programmes are reported in Table 8.

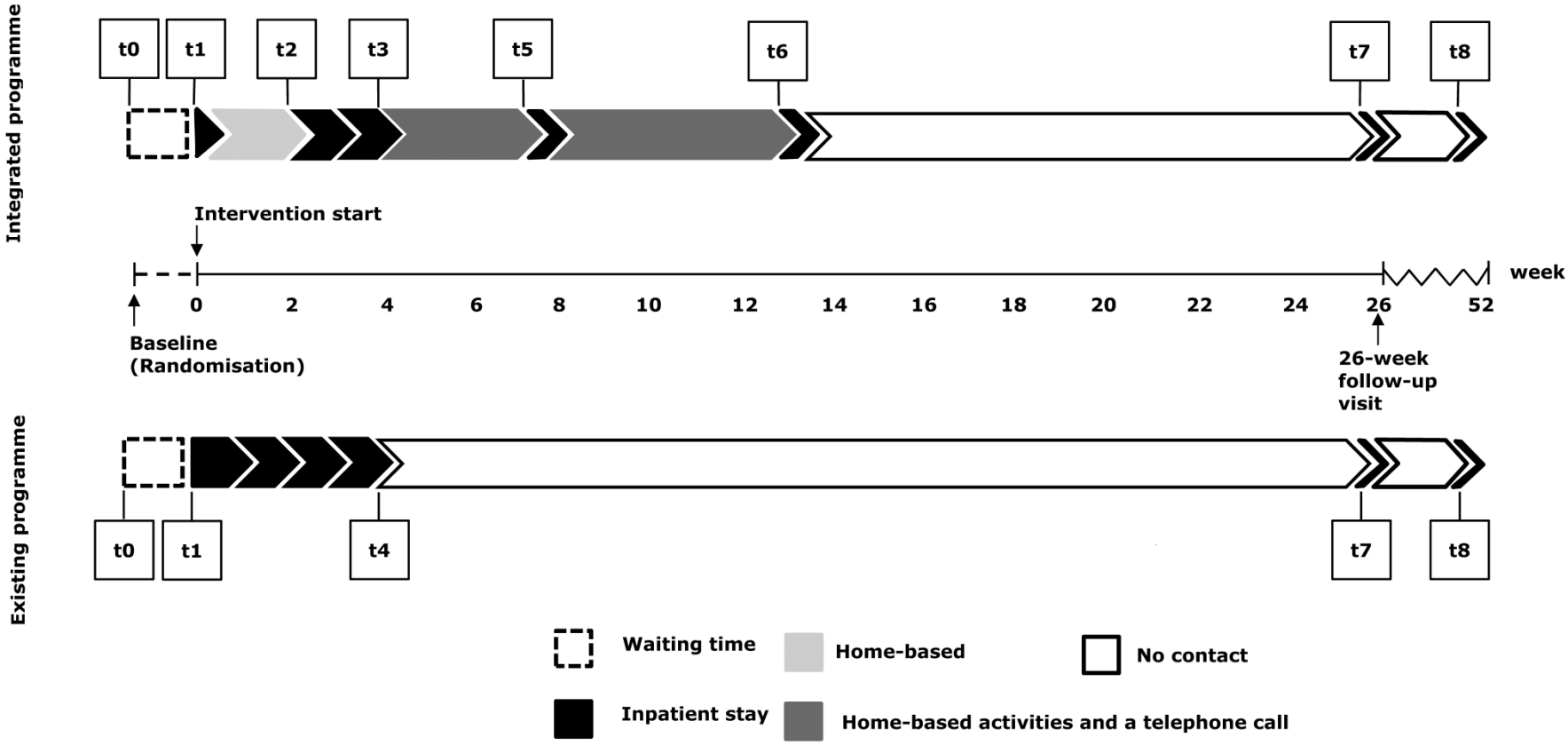


Figure 6. Comparison of the integrated programme and the existing programme (72).

Table 8. Differences and similarities between the integrated programme and the existing programme (72).

Differences		
Characteristics	Description	
	Integrated programme	Existing programme
Delivery of the rehabilitation programme	1) pre-admission day 2) two weeks of home-based activities 3) two-week inpatient stay 4) four weeks of home-based activities 5) initial two-day inpatient booster session 6) six weeks of home-based activities 7) second two-day inpatient booster session 8) 6-month follow-up visit In total 15 inpatient days. In between the inpatient stays, patients were at home (in total, 11 weeks). The integrated programme lasted for 14 weeks. During the integrated programme, continuous focus was on integration of knowledge, skills and behaviours into daily life supported by the home-based activities.	1) 4-week inpatient stay 2) 6-month follow-up visit In total, 21 inpatient days. The existing programme lasted for 4 weeks. At the end of the existing programme focus was on the integration of knowledge, skills and behaviours into daily life.
Elements to support integration of knowledge, skills and behaviours	- Pamphlet - A phone call half-way through each home-based period (in total, two phone calls) - Focus on integration during the inpatient stays, but especially in the clinical activities comprising individual counselling.	-
Development of the rehabilitation programme	A systematic research process following the MRC's guidance on developing and evaluating complex interventions.	Not developed using a systematic research process.
Patient and public involvement	A major part of the development, feasibility-test and evaluation.	-
Theoretical underpinning	The biopsychosocial approach and the Chronic Care Model.	The biopsychosocial approach.

Similarities	
Characteristics	Description
Rehabilitation programmes for patients with a variety of rheumatic health conditions	The rehabilitation programmes encompassed the four actions characterising the process of rehabilitation: 1) assessment, 2) goal setting, 3) intervention, and 4) evaluation (Section 1.4).
Clinical activities	38 clinical activities targeted the biopsychosocial factors driving disability. Some of the clinical activities were delivered more than once.
Providers	The multidisciplinary team consisted of six physiotherapists, three occupational therapists, three nurses (educated as coaches and primarily focusing on the psychologic aspect of the programme), a rheumatologist, and a nutritional counsellor. The majority of the providers were trained in the Motivational Interviewing approach.
Contact hours	Identical in the two rehabilitation programmes (approximately 50 contact hours).
Mode	A combination of group lecture and dialogue, group sessions (supervised and non-supervised), individual counselling and non-supervised individual exercise.
Setting	A rehabilitation centre in Denmark.
Tailoring	The rehabilitation programmes were partially standardised and partially tailored, the latter to ensure a degree of person-centeredness. The tailoring occurred primarily during: 1) the clinical assessment (including goal setting), 2) the multidisciplinary conference, 3) individual counselling, 4) exercise and physical activity, and 5) individual exercise (Table 3).
Additional contact	Permission to contact the providers twice via the exercise app.

4.2.5 Baseline characteristics, outcome domains, outcome measures, and other variables

Baseline characteristics comprised sex, age, marital status, smoking, leg pain, employment status and educational level.

The primary measurement time point was 6-month follow up (63). In addition, 1-year follow-up results were analysed (72) as the long-term effect of such a rehabilitation programme is interesting given that time is thought to be related to successful integration of knowledge, skills, and behaviours (31).

The choice of outcome domains and outcome measures was based on PPI in combination with international recommendations (80-83).

They were:

Primary outcome:

- Disability assessed by the ODI version 2.1a. ODI is a 10-item scale where each item contains six statements describing increasing degrees of disability. Each item is scored on a 0-5 point scale. The total score is doubled and expressed as a percentage; it is suggested rounding the percentage to a whole number. Minimum score is 0 and maximum score is 100; the higher the score the greater the disability (78). The index can be aggregated into five levels where 0-20% indicates minimal disability, 21-40% indicates moderate disability, 41-60% indicates severe disability, 61-80% indicates crippled and 81-100% indicates patients being bed-bound or exaggerating their symptoms (78). ODI has shown good psychometric properties (84).

Secondary outcomes:

- Pain intensity assessed by a Numerical Rating Scale (NRS) (80). It is scored on a 0-10 point scale where 0 defines absence of pain and 10 describes unbearable pain; the higher the score, the greater the pain disability (82). The NRS has shown good psychometric properties (83).
- Pain self-efficacy using the Pain Self-Efficacy Questionnaire (PSEQ). It consists of 10 questions about the patient's confidence in carrying out various normal activities despite pain. There are seven response options ranging from 0 (not at all confident) to 6 (very confident). The total score ranges from 0 to 60 points with higher scores indicating higher perceived pain self-efficacy (85). The psychometric properties of the PSEQ have been found to be sound (86).
- Health-Related Quality of Life (HRQoL) was measured by EQ-5D 5L ©, a generic questionnaire containing five dimensions each with five response options. The final score has a unique 5-digit descriptor corresponding to each dimension. Using a crosswalk value set for Denmark, health status was calculated and ranged between 1 (optimal health) and -0.624 (worst health); a high score indicates better HRQoL (87). EQ-5D 5L has not been tested in a LBP population (82, 83, 88).
- Depression using the Major Depression Inventory (MDI) as a depression rating scale covering the symptoms of depression (89) which contains 10 items scored on a 6 point Likert scale from 0 (at no time) to 5 (all the time); higher scores indicate a higher degree of depression. The individual items measure the proportion of time with present symptoms during the past two weeks (89). The MDI has shown adequate psychometric properties (89).

- Physical activity was identified by asking three questions (90):
  1) minutes spent in physical exercise during a typical week (0 minutes, less than 30 minutes, 30-59 minutes, 60-89 minutes, 90-120 minutes and more than 120 minutes).
  2) minutes spent in physical activity during a typical week (0 minutes, less than 30 minutes, 30-59 minutes, 60-89 minutes, 90-149 minutes, 150-300 minutes and more than 300 minutes).
  3) hours spent sitting in a typical 24-hour period (nearly the whole day, 13-15 hours, 10-12 hours, 7-9 hours, 4-6 hours, 1-3 hours, and never).
  The categories were slightly changed for the purpose of the RCT as the original categories were overlapping.
- Exercise capacity was measured by the Aastrand cycle test (91) using a calibrated bicycle (Monark 928 G3, Sweden) and performed by physiotherapists using a standardised performance-based protocol (92). There is moderate evidence of the reliability, validity and acceptability of the Aastrand cycle test in people with chronic pain (93).

Other variables:

- Cases of adverse events or death were extracted from electronic health records.
- Adherence was extracted from the electronic health records and defined as attending ≥ 80% of the scheduled inpatient days, based on reasoning. Thus, adherence was defined as attending ≥ 12 inpatient days in the integrated programme and attending ≥ 17 inpatient days in the existing programme. Adherence to the home-based activities was not measured.
- Waiting time was measured by counting days from baseline to the start of the rehabilitation programme.

4.2.6 Data collection

Data on baseline characteristics and outcome variables (except for exercise capacity) were collected using a battery of questionnaires.

In the integrated programme, data were collected: 1) at baseline (before randomisation) (t0), 2) before the pre-admission day (t1), 3) before the 2-week inpatient stay (t2), 4) at the end of the 2-week inpatient stay (t3), 5) before the initial booster session (t5), 6) before the second booster session (t6), 7) before the 6-month follow-up visit (t7), and 8) at 12 month follow up (t8) (Figure 6).

For the existing programme, data were collected: 1) at baseline (before randomisation) (t0), 2) before the 4-week inpatient stay (t1), 3) at the end of the 4-week inpatient stay (t4), 4) before the 6-month follow-up visit (t7), and 5) at 12 month follow up (t8) (Figure 6).

Patients were emailed the questionnaire link 10 days prior to the inpatient stay with a reminder after 5 and 8 days, if required. The research assistant ensured completion of questionnaires by handing out a tablet on the first inpatient day, if not completed beforehand. This procedure was repeated on the last inpatient day. Patients not attending a booster session, the 6-month follow-up visit and/or 12-month follow up were encouraged to complete the questionnaires via email. Patients unable to complete the electronic questionnaires were sent a paper version, which was double-entered into the database by the research assistant. The exercise capacity test was performed at the beginning of the 2-week (integrated programme) and the 4-week (existing programme) inpatient stay and, and again at the 6-month follow-up visit.

4.2.7 Statistical analyses

4.2.7.1 Sample size calculation

A difference in the change of 4 points in the ODI has been suggested as a minimum clinically important difference (78, 94). The sample size calculation for this RCT was based on an expected difference in change over time of 5 points on the ODI at the 6-month follow up (corresponding to a decrease of 10 points in the integrated programme compared to a decrease of 5 points in the existing programme (95)). The standard deviation (SD) was informed by our previous feasibility test including 12 patients attending the existing programme (SD on the difference of 10 points). With 80% power and a significance level of 0.05, 64 patients were required in each arm of the RCT, and allowing for lost to follow up of 20%, a total of 160 patients was needed.

4.2.7.2 Identical statistical analysis Studies 2 and 3

Descriptive statistics were presented with mean and SD or number and percentage depending on type of the variable.

Results were presented with 95% confidence intervals (CI) and p-values. A p-value ≤ 0.05 was considered statistically significant. For statistical analyses, STATA 15 (Study 2) and STATA 16 (Study 3) were used.

Statistical analysis plans was completed prior to the unblinding of data (Appendices 6 and 7).

4.2.7.3 Statistical analyses Study 2

Differences in sex, age and ICD-10 diagnosis codes were assessed for those patients randomised and those declining to participate. The primary analysis was a modified intention-to-treat (ITT) analysis according to originally allocated rehabilitation programme, excluding patients with missing outcome data at the 6-month follow up (complete case analysis). The between-group difference in mean change scores (integrated programme minus existing programme) from baseline to the 6-month follow up was analysed by multiple linear regression using change score as the dependent variable, rehabilitation programme as the independent variable, and the

corresponding baseline score as covariate. The within-group changes from baseline to the 6-month follow up were presented descriptively. Furthermore, the robustness of the complete case analysis in terms of the primary outcome was checked using ITT analysis with the last value carried forward. A per-protocol analysis was also conducted excluding patients who did not adhere to their rehabilitation programme. Finally, a secondary analysis including waiting time as a covariate was performed, as the process evaluation revealed that this variable by chance differed between the two rehabilitation programmes.

4.2.7.4 Statistical analyses Study 3

The primary analysis was an ITT analysis including the four similar measurement time point (t0, t1, t7 and t8). The effect of the rehabilitation programme on the primary and secondary outcomes was estimated by the difference in mean change between the two groups (integrated programme minus existing programme) from baseline to the 12-month follow up using a linear mixed model with a random intercept. The analysis included time (as a categorical variable), group and the interaction between group and time as explanatory variables. Furthermore, the linear mixed model was used to test if the development over time in the two rehabilitation programmes was similar (i.e. test of no interaction between group and time). The underlying assumptions behind a linear mixed model were checked by inspection of plots of random intercepts and residuals. For all outcomes except EQ-5D 5L and MDI, the assumptions were fulfilled, and hence the non-parametric bootstrap method with 1000 repetitions was used to compute p-values and 95% CIs for these two outcome measures. Three secondary analyses were conducted to examine the robustness of the primary analysis: 1) adding waiting time as a covariate, and 2) replacing missing values by the average of non-missing scores at the particular measurement time point, and 3) replacing missing values by the worst possible score (= 100) in the integrated programme and the best possible score (= 0) in the existing programme in an attempt to reveal a worst-case scenario. Additionally, graphs including means at all nine measurement time points (t0-t8) were presented to illustrate mean changes over time for each rehabilitation programme.

4.2.8 Ethical approval and trial registration

The Central Denmark Region Committees on Biomedical and Research Ethics approved the study (journal number: 1-10-72-117-16). The study was assigned an international trial identification number (ClinicalTrials.gov; identifier NCT02884466).

5. Results

In this chapter, the results from the three studies are reported. First, the results from Study 1 are reported. Next, patient flow and baseline characteristics from Studies 2 and 3 are reported together. Then the results from Study 2 are reported, followed by the results from Study 3. Finally, the findings from the process evaluation are reported.

5.1 Study 1

The justification and description of the integrated programme was presented in accordance with the TIDieR checklist (57). The description corresponds with how the integrated programme was when the RCT started.

5.1.1 Item 1. Brief name

The integrated programme.

5.1.2 Item 2. Why

The justification of the integrated programme was described in depth in Chapter 2.

5.1.3 Item 3. What (materials)

The facilities at the rehabilitation centre included classrooms, learning laboratories (e.g. a fully equipped kitchen), conversation rooms, a small hot water pool, and indoor and outdoor fitness facilities with cardio exercise equipment and strength training equipment.

A welcome pamphlet describing the clinical activities was emailed before the first inpatient day.

Most importantly, a pamphlet was provided that contained individualised preparation material focusing on the facilitation of goal-setting as well as physical and psychological preparation before the next inpatient stay.

5.1.4 Item 4. What (procedures)

Activity sheets describing each of the 38 clinical activities in detail are provided in Appendix 8. In Table 9, a completed activity sheet using aqua gymnastics as an example is shown.

The 38 clinical activities were grouped into 10 key components (Table 3). Further, the interrelationship between the 10 key components were illustrated by a web and the person-centred focus of the intervention was emphasised by giving the patient a central position (Figure 7).

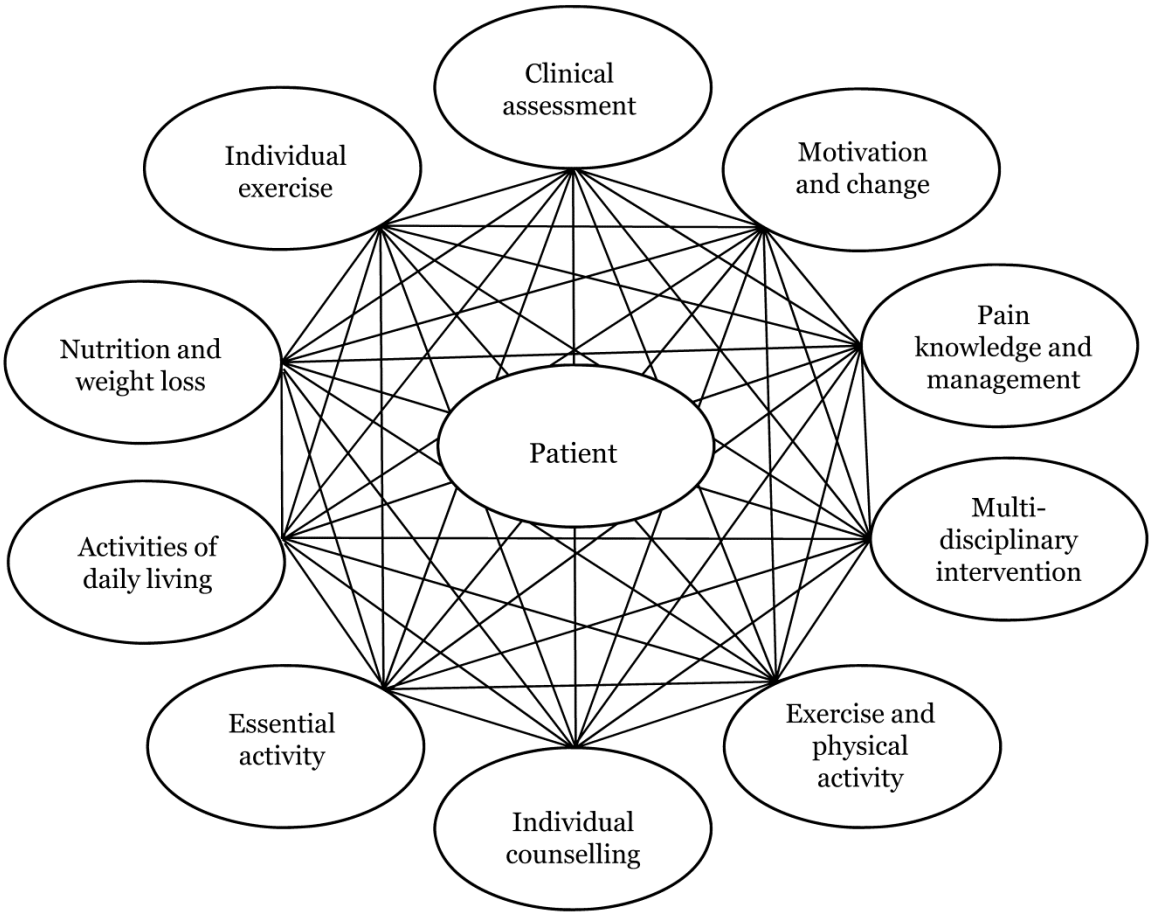


Figure 7. The interrelationship between the 10 key components.

5.1.5 Item 5. Who provided

The providers consisted of six physiotherapists, three occupational therapists, three nurses (educated as coaches and primarily focusing on the psychologic aspect of the programme), a rheumatologist, and a nutritional counsellor. The majority of the providers were trained in the Motivational Interviewing approach.

5.1.6 Item 6. How

The mode was a combination of theory and practice using group lecture and dialogue, group sessions (supervised and non-supervised), individual counselling and non-supervised individual exercise; all delivered face-to-face except for the non-supervised exercise.

To support the integration of knowledge, skills and behaviours into the daily life of the patients, a pamphlet (Section 5.1.3) and a telephone call during each of the last two home-based periods was scheduled. Furthermore, the patients were allowed and encouraged to contact the providers via an exercise app twice until the second booster session.

5.1.7 Item 7. Where

This item is reported in Section 4.2.2.

5.1.8 Item 8. When and how much

During the inpatient stays, 38 clinical activities were provided, some of them more than once. To illustrate the different sequence in which the clinical activities were delivered, a graphical depiction of the integrated programme and the existing programme was composed, inspired by a method developed for that purpose (96) (Appendix 9).

5.1.9 Item 9. Tailoring

The integrated programme was partially standardised and partially tailored, the latter to ensure a degree of person-centeredness. The tailoring occurred primarily during: 1) the clinical assessment (including goal-setting), 2) the multidisciplinary conference, 3) individual counselling, 4) exercise and physical activity, and 5) individual exercise (Table 3). Thus, what the individual patient received differed slightly as a result of tailoring.

5.1.10 Item 10. Modifications

This item is reported as part of the process evaluation (Section 5.5.1).

5.1.11 Item 11. How well (planned)

Adherence to inpatient days, time between inpatient stays, and adherence to the clinical activities was recorded in each patient's electronic health record.

5.1.12 Item 12. How well (actual)

This item is reported as part of the process evaluation (Section 5.5.5).

Table 9. The activity sheet developed to describe the 38 clinical activities; using aqua gymnastics as an example (57).

What (procedures) (Item 4)		Aqua gymnastics consisting of aerobic and anaerobic exercises as well as exercises focusing on mobility and stability/balance.
Tailoring (Item 9)		The exercises were chosen and adjusted based on the individual patient.
Who provided (Item 5)		Physiotherapist
How (Item 6)		Group session
When and how much (Item 8)	Number of sessions	Supervised: four sessions Non-supervised: six sessions
	Duration	30 minutes incl. warm-up and cool-down
	Intensity	Borg Scale of Perceived Exertion equaling 11-15

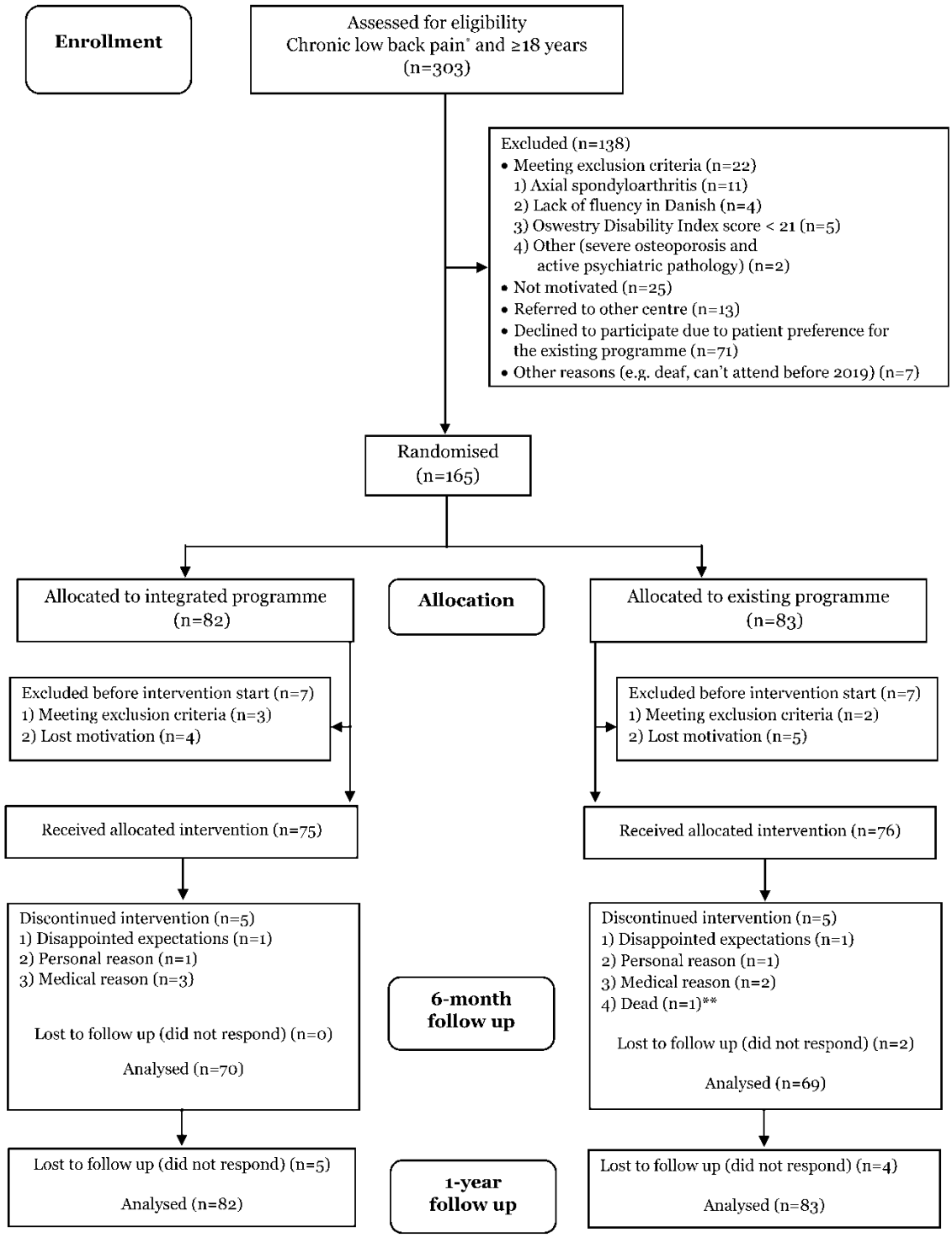
5.2 Patient flow and baseline characteristics in Studies 2 and 3

Recruitment and random allocation started in February 2016 and ended in August 2018. The first rehabilitation programme commenced in September 2016, and the last reached the 6-month follow up in May 2019 and 12-month follow up in November 2019.

In total, 303 patients were screened for eligibility, of whom 138 were excluded for various reasons. Those declining to participate (n = 71) did not differ from those randomised with respect to age (mean age 50, age range 22-79), sex (68% women) or diagnosis (data not presented). In total, 165 patients were randomly allocated to the integrated programme (n = 82) or to the existing programme (n = 83) (Figure 8).

There were no clinically relevant differences in baseline characteristics between patients lost to follow up and patients who completed the 6-month and 12-month follow up, respectively (data not shown).

At baseline, the patients had a mean age of 50 years (SD 13) and the majority (73%) of patients were women. The mean ODI score was 42 (SD 11) and the mean NRS score during the last two weeks was 6 (SD 2). Further baseline characteristics were also similar between the two rehabilitation programmes (Table 10).



* The following ICD-10 diagnosis codes for diseases, signs and symptoms related to chronic low back pain were used: DM40, DM41, DM42, DM43 (not 43.3, 43.4, 43.6), DM47, DM48, DM51, DM53 (not 53.0, 53.1), DM54 (not 54.0, 54.2, 54.6), DM96.1 and DT91.0.
** The reason for dead was unrelated to the trial.

Figure 8. Flow chart of patients in Studies 2 and 3. Combined from (63, 72).

Table 10. Characteristics of the population at baseline. Columns 1 and 2 show patients randomised (n = 165) and columns 3 and 4 show patients providing 6-month follow-up data (n = 139) (63).

	Patients allocated at baseline		**Patients providing 6-month follow-up data**	
	Integrated programme n = 82	Existing programme n = 83	Integrated programme n = 70	Existing programme n = 69
Sex (women) n (%)	60 (72%)	60 (73%)	52 (74%)	49 (71%)
Age (years)				
Mean (SD)	49 (13)	51 (13)	50 (12)	52 (12)
Range	22-72	25-84	28-72	25-84
Marital status n (%)				
Married	60 (73%)	58 (70%)	51 (73%)	50 (72%)
Single/widowed	22 (27%)	25 (30%)	19 (27%)	19 (28%)
Smokers n (%)				
Yes	24 (29%)	28 (34%)	17 (24%)	23 (33%)
No	58 (71%)	55 (66%)	62 (76%)	46 (67%)
Leg pain n (%)				
Yes	65 (79%)	59 (71%)	55 (79%)	49 (71%)
No	12 (15%)	17 (21%)	12 (17%)	14 (20%)
Don't know	5 (6%)	7 (8%)	3 (4%)	6 (9%)
Employment status* n (%)				
Self-supporting	17 (26%)	16 (25%)	17 (30%)	15 (29%)
Temporary social benefits	9 (14%)	11 (17%)	7 (13%)	8 (15%)
Permanent social benefits	29 (45%)	27 (42%)	24 (43%)	20 (39%)
Age-related pension	8 (12%)	10 (16%)	7 (13%)	9 (17%)
Others	2 (3%)	0 (0%)	1 (2%)	0 (0%)
Education level*				
Low (≤12 years)	10 (15%)	14 (22%)	6 (11%)	11 (21%)
Middle (≤16 years)	44 (68%)	44 (69%)	40 (71%)	36 (69%)
High (> 16 years)	11 (17%)	6 (9%)	10 (18%)	5 (10%)
Disability ODI (0-100)**				
Mean (SD)	42 (10)	43 (11)	41 (11)	43 (12)
Range	20-68	24-72	20-68	24-72
Back pain intensity* NRS (0-10)**				
Mean (SD)	6 (2)	6 (2)	6 (2)	6 (2)
Pain Self-efficacy PSEQ (0-60)				
Mean (SD)	28 (11)	27 (10)	28 (12)	27 (11)
HRQoL EQ-5D 5L (-0.624-1)				
Mean (SD)	0.567 (0.157)	0.603 (0.118)	0.578 (0.153)	0.599 (0.126)
Depression MDI (0-50)				
Mean (SD)	20 (12)	20 (11)	19 (11)	22 (11)

	Patients allocated at baseline		Patients providing 6-month follow-up data	
	Integrated programme n = 82	Existing programme n = 83	Integrated programme n = 70	Existing programme n = 69
Physical activity n (%)				
Minutes spent in physical exercise during a week				
< 30	42 (51%)	50 (60%)	34 (49%)	41 (59%)
≥30 ≤ 120	32 (39%)	31 (37%)	28 (40%)	26 (38%)
> 120	8 (10%)	2 (3%)	8 (11%)	2 (3%)
Minutes spent in physical activity during a week				
< 30	13 (16%)	20 (24%)	9 (13%)	17 (25%)
≥30 ≤ 300	52 (63%)	55 (66%)	45 (64%)	45 (65%)
> 300	17 (21%)	8 (10%)	16 (23%)	7 (10%)
Hours spent sitting in 24-hour period				
≥ 10	9 (11%)	14 (17%)	7 (10%)	6 (9%)
<10 ≥4	53 (65%)	52 (63%)	47 (67%)	51 (74%)
<4	20 (24%)	17 (20%)	16 (23%)	12 (17%)

*Due to technical issues in the database, data on employment status and education level was only available in ≈ 75% of the patients.
**Due to technical issues in the database, one patient with an ODI score of 20 was included.
***Mean back pain intensity during the last two weeks.
ODI: Oswestry Disability Index; NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; HRQoL: Health-Related Quality of Life; EQ-5D 5L: EuroQol-5 Domain 5-level; MDI: Major Depression Inventory

5.3 Results Study 2

At 6-month follow up (63), the complete case analysis included 70 patients allocated to the integrated programme and 69 patients allocated to the existing programme, thus 12 patients in the integrated programme and 14 patients in the existing programme were lost to follow up (Figure 8).

The between-group difference in the mean change in ODI score revealed an estimate of -0.28 (95% CI: -4.02; 3.45) being neither statistically nor clinically significant (Table 11). Nor were there any statistically significant between-group differences in mean change in the secondary outcomes (Table 11).

Data on physical activity was omitted from the analysis due to post hoc awareness of inadequacies of the three questions measuring it (this issue is also relevant to Study 3). The inadequacies consisted of overlap of categories, the intervals between the categories not being linear, and question 3 (the number of hours spent sitting) was deemed of less relevance in a CLBP population where the alternative to sitting could be lying.

Among those allocated to the integrated programme, the average decrease in ODI scores was from 42 (95% CI: 39; 44) at baseline to 36 (95% CI: 33; 39) at the 6-month follow up. Among those allocated to the existing programme, the average ODI score decreased from 43 (95% CI: 40; 45) at baseline to 37 (95% CI: 34; 40) at the 6-month follow up.

Some secondary analyses were performed. Firstly, on average, patients in both rehabilitation programmes improved on all outcomes (within-group) (Table 11). Secondly, the ITT analysis on the ODI with the last value carried forward did not change the result (mean difference: 0.90 (95% CI: -2.63; 4.44), p-value = 0.614). Thirdly, including waiting time as a covariate did not change the result either (mean difference: -0.92 (95% CI: -4.73; 2.89), p-value = 0.633).

Lastly, no related adverse events or deaths occurred due to the RCT (this issue is also relevant to Study 3).

Table 11. Summary of 6-month follow-up data on primary and secondary outcomes. Between-group and within-group change; complete case analysis (63).

	Between-group*		**Within-group**	
			Integrated programme (n = 70)	Existing programme (n = 69)
	Mean (95% CI)	p-value	Mean (95% CI)	Mean (95% CI)
Primary outcome				
Disability (ODI)	-0.28 (-4.02 ; 3.45)	0.881	-5.76 (-8.31 ; -3.20)	-5.64 (-8.45 ; -2.83)
Secondary outcomes				
Pain intensity** (NRS)	-0.02 (-0.64 ; 0.59)	0.937	-0.76 (-1.21 ; -0.31)	-0.64 (-1.08 ; -0.19)
Pain Self-Efficacy (PSEQ)	0.05 (-3.47 ; 3.57)	0.978	6.01 (3.48 ; 8.80)	6.22 (3.63 ; 8.80)
HRQoL (EQ-5D 5L)	0.01 (-0.03 ; 0.05)	0.670	0.05 (0.02 ; 0.08)	0.03 (0.00 ; 0.07)
Depression (MDI)	0.62 (-1.98 ; 3.21)	0.639	-3.3 (-5.27 ; -1.24)	-4.57 (-6.52 ; -2.62)

*Adjusted for corresponding baseline value. Existing programme as reference group.
**Mean pain intensity during the last two weeks.
ODI: Oswestry Disability Index; NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; HRQoL: Health-Related Quality of Life; EQ-5D 5L: EuroQol-5 Domain 5-level; MDI: Major Depression Inventory

5.4 Results Study 3

At the 12-month follow up (72), a mean between-group difference in change of -0.53 (95% CI: -4.08 to 3.02) was found in the ODI score; this was neither statistically nor clinically significant (Table 12 and Figure 9). Furthermore, no evidence of a difference in development in ODI score over time was found ($\chi^2(3) = 0.12$, p-value = 0.989) (Figure 9).

Similarly, no statistically significant between-group differences were found for any of the secondary outcomes (Table 12 and Figure 10).

Table 12. Summary of 12-month follow-up data on primary and secondary outcomes. Between-group and within-group change; intention-to-treat analysis (72).

	Between-group		**Within-group**	
	Mean difference* (95% CI)	p-value	Integrated programme Mean (95% CI)	Existing programme Mean (95% CI)
Primary outcome				
Disability (ODI)	-0.53 (-4.08 ; 3.02)	0.770	-4.55 (-7.08 ; -2.02)	-4.02 (-6.51 ; -1.53)
Secondary outcomes				
Pain intensity** (NRS)	-0.10 (-0.68 ; 0.48)	0.727	-0.58 (-1.00 ; -0.17)	-0.48 (-0.89 ; -0.07)
Pain Self-Efficacy (PSEQ)	0.01 (-3.34 ; 3.37)	0.994	4.43 (2.05 ; 6.82)	4.42 (2.07 ; 6.78)
HRQoL (EQ-5D 5L)***	0.02 (-0.04 ; 0.07)	0.558	0.04 (0.00 ; 0.07)	0.02 (-0.01 ; 0.06)
Depression (MDI)***	1.67 (-1.52 ; 4.85)	0.305	-1.79 (-3.96 ; 0.38)	-3.45 (-5.80 ; -1.11)

*Mean difference = integrated – existing
**Mean pain intensity during the last two weeks
***When analyzing EQ-5D 5L and MDI non-parametric bootstrap method with 1000 repetition two compute p-values and 95% CI's was used.
ODI: Oswestry Disability Index; NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; HRQoL: Health Related Quality of Life; EQ-5D 5L: EuroQol-5 Domain 5-level; MDI: Major Depression Inventory

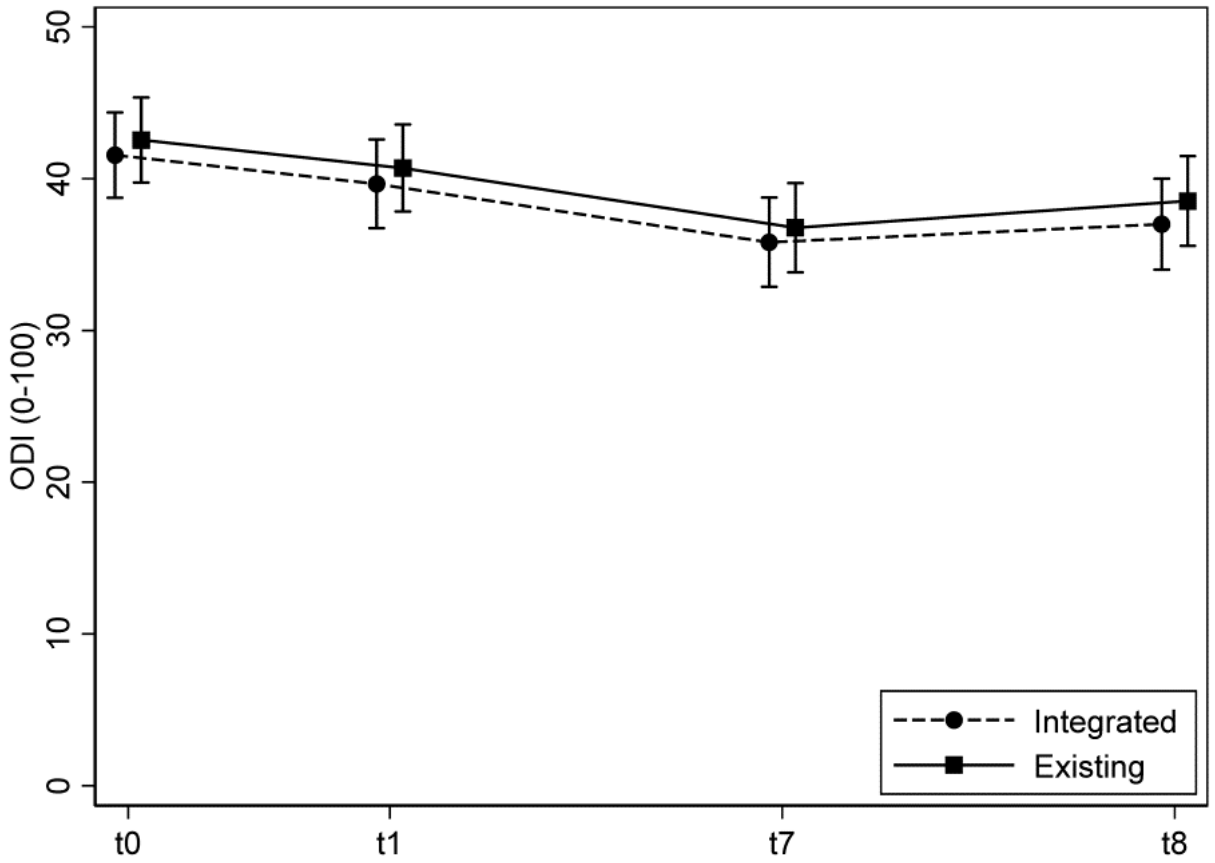


Figure 9. Mean change in back-specific disability measured by the Oswestry Disability Index (ODI) during the 12-month follow-up period, including the four identical measurement time points: t0 = baseline, t1 = before intervention start, t7 = before the 6-month follow-up visit, and t8 = the 12-month follow up (from the linear mixed model). The time between t0-t1 was 4 months (= mean waiting time), the time between t1-t7 and between t7-t8 was 6 months. (72)

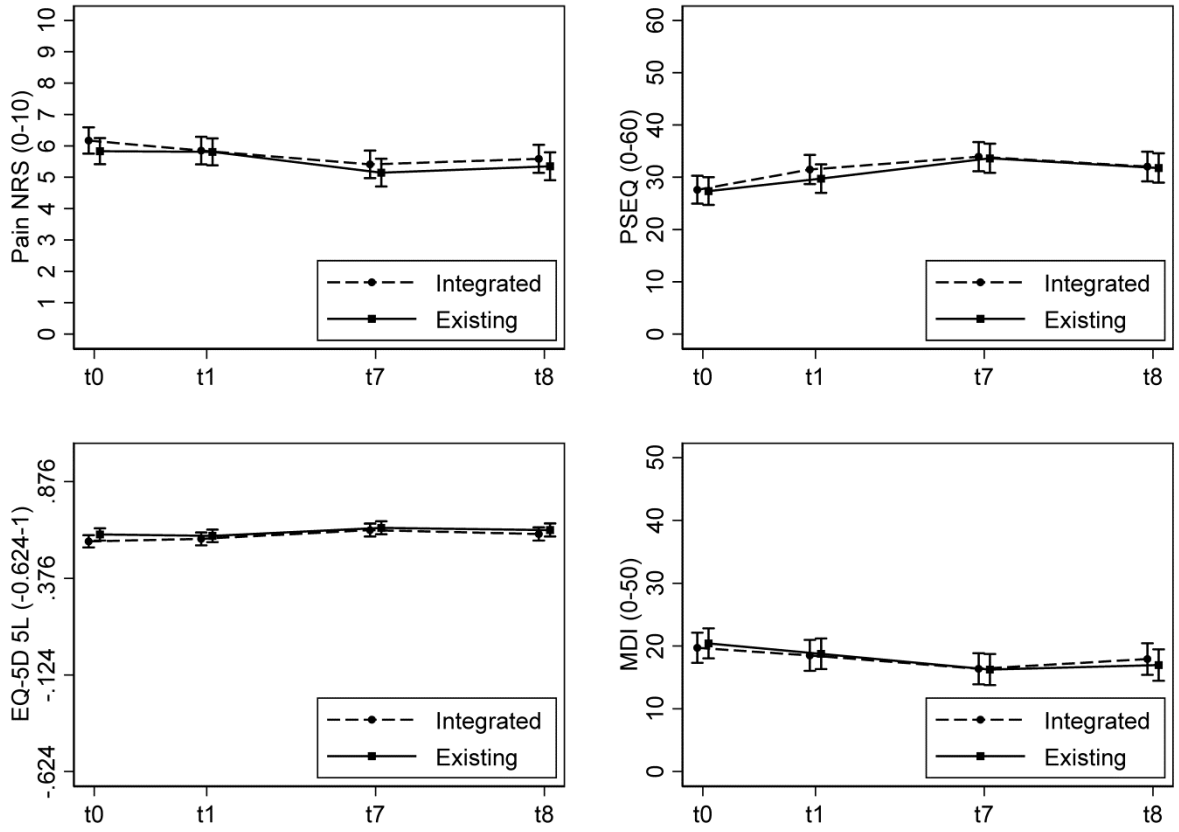


Figure 10. Mean changes in secondary outcomes during the 12-month follow-up period including the four identical measurement time points: t0 = baseline, t1 = before intervention start, t7 = before the 6-month follow-up visit, and t8 = the 12-month follow up. The time between t0-t1 was 4 months (= mean waiting time), the time between t1-t7 and between t7-t8 was 6 months.
NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; EQ-5D 5L: EuroQol-5 Domain 5-level; MDI: Major Depression Inventory. (72)

Among those allocated to the integrated programme, the average decrease in ODI scores was from 42 (95% CI: 39; 44) at baseline to 37 (95% CI: 34; 40) at the 12-month follow up. Among those allocated to the existing programme, the average ODI score decreased from 43 (95% CI: 40; 45) at baseline to 39 (95% CI: 36; 41) at the 12-month follow up.

Within-group improvements were found on most outcomes, except for depressive symptoms in the integrated programme and HRQoL in the existing programme (Table 12).

The secondary analysis adjusted for waiting time did not change the result (mean difference: -0.41 (95% CI: -4.02; 3.20), p-value = 0.824). Neither did the secondary analysis replacing missing values by the average of non-missing scores at the particular time point (mean difference: -0.60 (95% CI: -3.78; 2.58), p-value = 0.712). Finally, the secondary analysis replacing missing

values with the worst possible ODI score (= 100) for the integrated programme, and by the best possible ODI score (= 0) for the existing programme, changed the results (mean difference: 19.79 (95% CI: 13.80; 25.77), p-value = 0.000).

The outcome trajectories, including all measurement time points from t0-t8, revealed that changes over time were similar in the two rehabilitation programmes, regardless of which outcome measure was chosen (Figure 11).

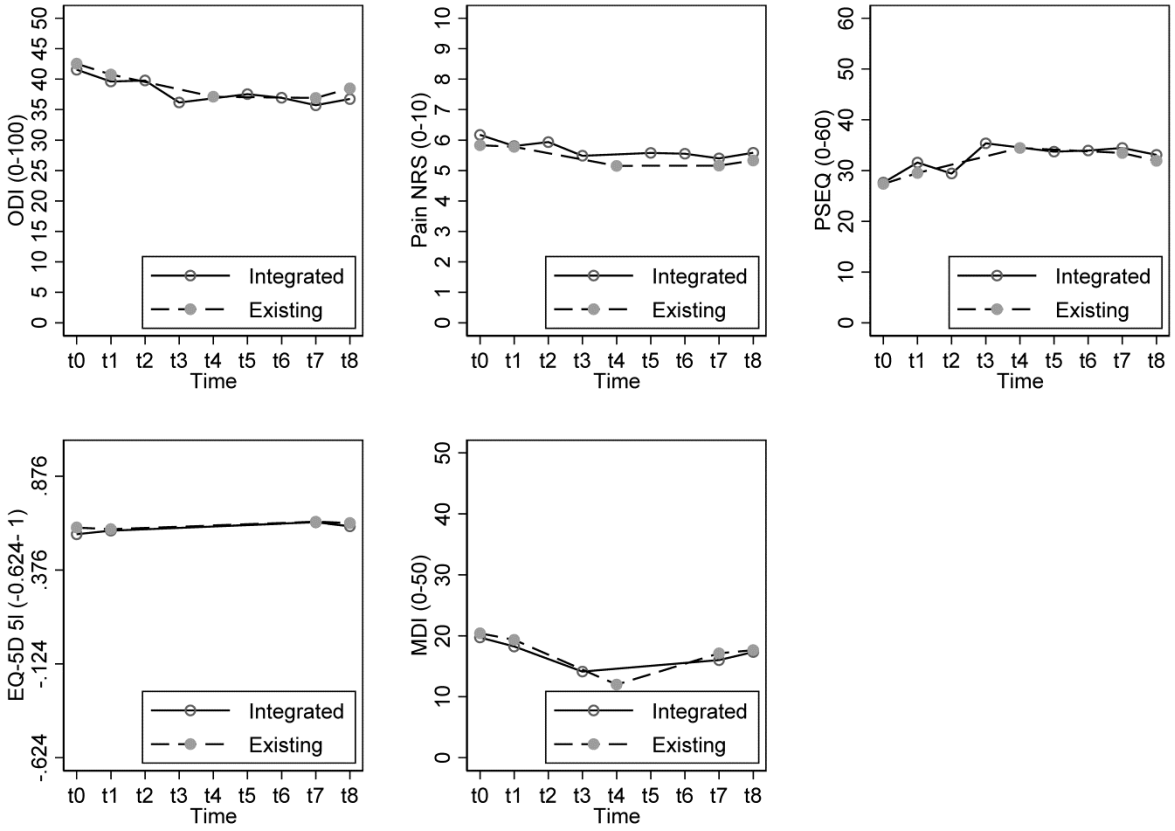


Figure 11. Mean changes over the 12-month follow up-period, including all nine measurement time points (t0-t8). Notice that the distances between the measurement time points are displayed as equidistant even though they were not. t0 = baseline, t1 = before the pre-admission day (integrated programme) and before the 4-week inpatient stay (existing programme), t3 = the end of the 2-week inpatient stay (integrated programme), t4 = the end of the 4-week inpatient stay (existing programme), t5 = before the initial booster session (integrated programme), t6 = before the second booster session (integrated programme), t7 = before 6-month follow-up visit (integrated programme + existing programme), and t8 = the 12-month follow up (integrated programme + existing programme).
ODI: Oswestry Disability Index; NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; EQ-5D 5L: EuroQol-5 Domain 5-level; MDI: Major Depression Inventory. (72)

5.5 Process evaluation

5.5.1 Process research question 1

"*Was the integrated programme modified during the trial?*"

Yes, it was modified, and the most relevant modifications were:

- Employment of a psychologist in September 2017.
- Change in the number of hours of aqua gymnastics from April 2018 (from 1 hour and 25 minutes per week to 1 hour per week). Furthermore, the setting was changed from the rehabilitation centre's own hot water pool to a public hot water pool.
- Continuous challenges with implementing the exercise capacity test.

The modifications were identical to modifications in the existing programme.

5.5.2 Process research question 2

"*What relevant changes to referral, administration, management etc. occurred during the trial?*"

The most relevant changes were:

- Postponement of allocated inpatient stays initiated by the patients. This caused a more or less persistent low number of patients attending most of the integrated programmes despite overbooking. Therefore, fewer integrated programmes were scheduled in the last part of the RCT.
- Low adherence to the 6-month follow-up visit reaching approximately 20% non-adherence in each rehabilitation programme.

Examples of modifications to the integrated programme (process research question 1), and relevant changes to referral, administration, management etc. (process research question 2) were reported collectively in Appendix 10.

5.5.3 Process research question 3

"*The stakeholders' experiences with and perspectives of the integrated programme*".

Findings from a Masters student's interview with the stakeholders in February 2018 are briefly summarised below.

The stakeholders:

- Felt involved in the development of the integrated programme.
- Had positive expectations about the integrated programme – though when implementing it, the overall aim (integrating knowledge, skills and behaviours) got lost in daily clinical

practice, and they felt that they either had to justify or apologise for the design of the integrated programme without being able to explain the overall aim to the patients.
- Emphasised the pamphlet and phone calls as important elements, nevertheless, they felt that using these supportive elements reduced time for other important tasks in daily clinical practice.
- Expressed concerns about whether they were able to make an actual difference to patients attending the integrated programme e.g. due to time spent on re-connecting with patients and on follow-up talks.
- Comparing the two rehabilitation programmes, they favoured the existing programme, as they were concerned about the differences in group cohesion, the different time periods to disconnect from daily lives, and the different abilities to informally recap with patients attending the integrated programme.

5.5.4 Process research question 4

"The patients' experiences with the integrated programme and with integrating the programme into their daily life".

Findings from a Masters student's interview with patients in February 2019 are briefly summarised below.

The patients:

- Had various opinions on the delivery of the integrated programme; some found the inpatient days too compressed, whereas others felt they had too much time on their own; some felt there were too few inpatient days and wondered if the integrated programme was effective enough, whereas others found the combination of inpatient days and home-based activities meaningful in terms of their personal life.
- Felt that the alternation between inpatient stays and home-based activities, as well as the phone calls, provided them with relevant feedback and motivation, and for that reason, they experienced a relevant transition from the inpatient stays to their daily life. In contrast, some patients did not feel that they succeeded in integrating their efforts into their daily life.
- Profited from the group cohesion.
- Experienced that the efforts by the providers were meaningful, and they felt seen, heard and understood while attending the integrated programme.
- Felt that they were able to accept their situation and disability after attending the integrated programme.

5.5.5 Process research question 5

"Was the integrated programme delivered as planned?".

Yes, it was delivered as planned. Adherence to the inpatient days was excellent in both rehabilitation programmes, as the majority of patients attended ≥ 80% of the inpatient days, shown by 99% of the patients in the integrated programme, and 100% of the patients in the existing programme. For that reason, the pre-specified per-protocol analysis in Study 2 was deemed unnecessary.

5.5.6 Process research question 6

"Did waiting time differ between the two programmes?"

Yes, by chance, waiting times differed between the two rehabilitation programmes with a mean of 105 days (SD 9) in the integrated programme and a mean of 141 days (SD 10) in the existing programme.

6. Discussion

This chapter begins with a section reflecting on substantial elements of the integrated programme including Study 1. Next, the PPI process is discussed. Following that, the main results from the RCT (Studies 2 and 3) are discussed in two parts. In part one, the main results will be compared with the literature, and in part two, the main findings from the process evaluation will be discussed in relation to the main results from the RCT. Finally, strengths, limitations and external validity will be discussed.

6.1 Reflections on the integrated programme including Study 1

To ensure a systematic approach, this section is divided into subsections following the stages outlined in the MRC's guidance (32) (Figure 1). Those of the 12 related elements in the MRC's guidance considered important for discussion are *italicised*.

6.1.1 Development stage

Considering *Identifying the evidence base* and *Identifying/developing theory*. The justification of this RCT was described in Study 1 based on the evidence, and the underlying theories being the biopsychosocial approach and the Chronic Care Model (57). The applicability of those theories could rightly be questioned given the null effect. While the biopsychosocial approach, responding to the aetiology of CLBP has been widely accepted and scientifically endorsed since the 1980s (15, 16, 18-20), the Chronic Care Model (51-53) does not have quite the same evidence base when it comes to musculoskeletal conditions (48, 97-100). The latter will be further elaborated in Section 6.3.

Considering *Modelling processes and outcomes*. Two aspects need elaboration, namely the detailed description of the integrated programme following the TIDieR checklist (58) published as Study 1 (57), and the chosen outcome domains and outcome measures.

Firstly, the experiences using the TIDieR checklist (58) ensured a systematic, detailed description of the integrated programme. As part of the description, activity sheets were developed (Table 9), allowing us to structure and standardise the description of each of the 38 clinical activities. Further details, e.g. about the specific exercises, could have been added. However, it was the type of clinical activities rather than the details about each of them that we wanted to capture and describe (101). Furthermore, it would have been ideal to describe the evidence and/or theory behind each of the 38 clinical activities, and add it either to the activity sheets and/or to the logic model. However, the clinical activities were designed to support and enhance each other (Table 3 and Figure 7), and it was the bundle of clinical activities, and not one specific clinical activity, that we wanted to assess (31). For this reason, the evidence and/or theory behind each clinical activity was not described.

Secondly, disability was chosen as the preferred outcome domain based on a combination of results from the PPI process and the international recommendations about core outcomes for trials in the field of LBP (81, 82). It could be argued that measuring the domain of integrating knowledge, skills, and behaviours into daily life, which was the intended target of the integrated programme, would have been more appropriate. To our knowledge, no outcome measure to capture this specific domain has been developed and validated. Therefore, disability was chosen as a proxy for this integration even though the relationship between disability and integration of knowledge, skills, and behaviours is unknown. Based on its widespread use and endorsement (80, 82) together with its validity (78), the ODI seemed an appropriate outcome measure.

An alternative outcome measure could have been the Patient Activation Measure (PAM) which assesses the domain of patient knowledge, skill, and confidence required for self-management (102). The use of the PAM in a CLBP population has been sparsely investigated, and the Danish version of the PAM has only been validated in patients with dysglycaemia (102). For these reasons, the PAM was considered irrelevant in this RCT.

Pain self-efficacy is a psychological domain (2) that seeks to capture a person's expectation to perform a particular behaviour or task, and their confidence in being able to do so despite pain (86). The domain of pain self-efficacy may be closer to the domain of integrating knowledge, skills, and behaviours, than the domain of disability. Despite that, no difference in pain self-efficacy was found between the two rehabilitation programmes, albeit the RCT was not powered to detect differences in this outcome.

Given the broad biopsychosocial dimensions of the chosen outcomes, and the consistent finding of no between-group differences in this RCT, it is unlikely that the results of the RCT would have been any different using any other outcomes.

6.1.2 Feasibility/piloting

Considering *Testing procedures*. With the value of hindsight, running a pilot RCT would have been preferable, as it could possibly have revealed (some of) the unexpected challenges established in the process evaluation.

Considering *Determining sample size*. As described in Section 4.2.7.1, the literature suggests a 4-point between-group difference in change as being of minimum clinically importance (78, 94). At the time we calculated our sample size, no RCTs comparing two or more rehabilitation programmes had used the ODI as a primary outcome measure, and only one RCT comparing a rehabilitation programme to outpatient physiotherapy had used the ODI in an RCT (95). The RCT found a 9-point decrease on the ODI at the 6-month follow up following a 3-week ambulatory programme from Monday to Friday, and a 4-point decrease on the ODI following outpatient

physiotherapy (95). Thus, we found it reasonable to detect a 10-point decrease in ODI at the 6-month follow up following participation in the integrated programme, and a 5-point decrease in ODI at the 6-month follow up following participation in the existing programme. The SD of the difference was estimated at 10 points, informed by our previous feasibility-test. This is at the lower end compared with that reported in the literature that estimates SD to be between 10-21 points in a population of patients with CLBP when using the ODI (78). Collectively, the chosen estimates correspond to an effect size of 0.5, which could be considered too ambitious in light of an effect size at 0.23 when pooling 16 RCTs comparing rehabilitation with usual care (7). In contrast, comparing two comprehensive rehabilitation programmes with an estimated effect size of 0.5 could be considered reasonable in light of an effect size of 0.68 when pooling 19 RCTs comparing rehabilitation with physical treatment (7). The same rationale and an estimated between-group difference in change of 5 points on the ODI was used in an RCT from 2018, comparing two rehabilitation programmes at the 12-week follow up (103), which supports our estimation. Finally, we were less ambitious than another RCT from 2018 comparing two rehabilitation programmes that looked for a between-group difference of 8 points on the ODI at the 12-month follow up (104). For practical reasons we had to allow for a degree of pragmatism by making a realistic estimation based on potentially eligible patients, inclusion- and exclusion criteria, and the number of patients willing to participate and complete the RCT (79).

6.1.3 Evaluation stage

Considering *Assessing effectiveness*. A single-centre, pragmatic, two-arm parallel RCT was chosen as an appropriate design to assess effectiveness. Strengths and limitations of this design will be discussed in Section 6.5, except for the pragmatic attitude and the related PRECIS-2 score, which will be discussed here.

To assess the degree to which the self-identified pragmatic attitude of our RCT was truly so, the PRECIS-2 tool was used retrospectively. Had the assessment been done prospectively, the scores would probably have been slightly different, especially in relation to domain 4 (Organisation). Prospectively, it was expected that the integrated programme could easily be adapted to the usual organisation, thus, an a priori score would probably have been 5. Retrospectively, it was learned that the integrated programme did not just fit in to the usual workflow at the rehabilitation centre; e.g. the realisation that the pamphlet and phone calls were new elements to the providers and not easily implemented, and the administrative changes related to booking. For these reasons, the retrospective score was 3 (Table 7 and Figure 5). Despite this difference between the hypothesised prospective and the actual retrospective score, the PRECIS-2 assessment is still thought to be useful to stakeholders when understanding applicability of the results (105). Considering and scoring design choices (Table 7) and depicting them in the PRECIS-2 wheel (Figure 5) confirmed

that the design was primarily pragmatic, thus, we were able to answer questions about real-world effectiveness (73, 74, 105).

Considering *Understanding change processes*. In the following, the methods used in the process evaluation will be discussed. The findings from the process evaluation and their relationship with the RCT results will be discussed in Section 6.4.

No gold standard exists as how to design and conduct a process evaluation (41, 43). The choice of process research questions and the methods used to clarify them in this research project were explicitly presented as recommended (43) (Figure 4). Ideally, it could have been valuable to address the experiences of patients attending the existing programme. Many other process research questions could have been addressed as well, but it is considered preferable to answer a few closely selected process research questions thoroughly than to answer several poorly (41, 61).

In this research process, the PhD candidate analysed the process data before the outcome data. Arguments exist for both separation and integration of the process evaluator and the outcome evaluator (42). A disadvantage of integration is the risk of inducing biased interpretations of the outcome data (42). Thus, the PhD candidate was blinded when performing the analyses of outcome data. It was impossible for the PhD candidate to be independent of the RCT when analysing the process data, and therefore, it is seen as a strength that two Masters students performed the in-depth analyses of process research questions 3 and 4. An advantage of the integration is that the PhD candidate was close enough to the clinic to record the problems and understand why they occurred, as well as being able to contribute with effective solutions to the problems in collaboration with the stakeholders.

In terms of the process evaluation, some essential methodological considerations relate to: 1) recruitment of patients and stakeholders, and 2) timing of data collection (41, 42).

Firstly, in terms of process research question 4, patients from different groups were included, and process research questions 1, 2 and 3 included every stakeholder employed at the rehabilitation centre. The broad inclusion of different groups of patients and every stakeholder was thought to give a wide perspective on implementation, mechanisms of change, and context affecting and interacting with the integrated programme.

Secondly, process research questions 1, 2 and 4 were addressed at multiple time points. The in-depth assessment of process research questions 3 and 4 were performed at a single time point for practical reasons. Data collection at multiple times points is valuable as experiences and perceptions may shift over time, and the conclusions drawn will be situated in the time in which they were collected (41, 42).

Some of the data gathered from the process evaluation were formative, being reported back quickly in order to improve the quality of the integrated programme, and some of it was summative, being reported after the evaluation of the RCT to help understand the effectiveness of the integrated programme (61). Each attempt to improve the quality of the integrated programme (e.g. the attempts to support implementation of the pamphlet, the phone calls, and the exercise capacity test) was openly documented in a process evaluation document (Appendix 10). For that reason, the potential improvements were not thought to compromise the results nor the external validity (41, 42).

In all, the systematic, rigorous and transparent approach to the process evaluation is considered to improve the validity of the RCT results (43).

Considering *Assessing cost-effectiveness*. Due to the time frame of the research project, an economic evaluation was not conducted even though it certainly could have contributed with an important aspect, and thus, made the results more useful for decision-makers (32). By choosing the EQ-5D as a secondary outcome measure, the possibility for an economic evaluation remains.

6.2 PPI

PPI was not incorporated into this research project according to a pre-specified plan. The project team had little experience, and neither the patients nor the stakeholders had any experience with PPI in research. Research training was not done, and whether to perform it or not is widely discussed (66, 106). Despite that, we experienced that all patients had introspection and were able to be critical in a constructive way, thus contributing with their lived experiences rather than being "professional patient representatives". The PhD candidate facilitated and encouraged PPI to the best of her ability, but she was not specifically trained in this. Fortunately, the collaboration became two-way, as patients and stakeholders addressed the PhD candidate directly if they had ideas or insights they wanted to share. This maintained a continuous connection to knowledge, perspectives and lived experiences obtained in daily clinical practice.

Evidence regarding the impact of PPI remains weak (107), but PPI is thought to reduce research waste, and is proposed to be done for moral reasons (65). It is definitely the experience that PPI has improved the current research project by offering new ideas, improving understanding of patients' and stakeholders' perspectives, and thus, helped us to identify and hopefully avoid problems we might not have anticipated.

6.3 Main results from the RCT compared with the literature

Remembering that the optimal dose, content or delivery of a multidisciplinary rehabilitation programme remain unknown (7) (Chapter 1), the results from Studies 2 and 3 will be compared with those reported in the literature. Firstly, the results will be compared with the evidence base

consisting of RCTs comparing two or more rehabilitation programmes in patients with CLBP. Secondly, the results will be compared with the findings from RCTs assessing the effect of booster sessions in the musculoskeletal field.

To our knowledge, this is the first RCT comparing two different ways of delivering a rehabilitation programme while keeping the content stable. Six RCTs, with a total sample size of 945 participants, were of special interest when undertaking comparison with our results (46-49, 103, 104). The similarities between the six RCTs and our RCT were that they included CLBP patients, they compared two or more different rehabilitation programmes, and they used disability as the primary outcome domain. However, they had some substantial differences:

- The populations included had different levels of disability at baseline (46-49, 103, 104).
- Four different outcome measures were used to measure disability, namely the ODI (103, 104), the Roland Morris Disability Questionnaire (46, 49), the Quebec Back Pain Disability Scale (47), and the Pain Disability Index (48).
- Some of the RCTs compared different dose and content (47, 49, 103), and some compared identical rehabilitation programmes plus an additional component in one programme e.g. involvement of spouses (46), more specifically tailored interventions (104), or subsequent booster sessions (48). The last-mentioned RCT was referred to in Chapter 2, as it was the only previous RCT in the CBLP field aiming to assess the effect of adding booster sessions (seven phone calls) (48).
- Two RCTs used short-term follow up (3 months or less) (103, 104), two RCTs used medium-term follow up (3 to less than 12 months) (47, 49), and yet four RCTs incorporated long-term follow up (12 months or more) (46, 48, 49, 104).

These differences limit direct comparison with our RCT. However, regardless of the differences, the results of the six RCTs were similar to the current RCT, and found no significant differences in disability when comparing two or more rehabilitation programmes.

In general, evidence supports that rehabilitation is a beneficial process (33). As well, when it comes to research into rehabilitation and CLBP, evidence supports the effect of rehabilitation (7, 14, 22-24). However, when adding our results to the current evidence base in the CLBP research field, it is obvious that there is an unsolved Gordian knot, as it seems difficult to demonstrate if and how much dose, content and delivery of a specific rehabilitation programmes matters (33). It could be discussed whether the reasons for the repeated null effect in the RCTs could be due to sample sizes, differences in population, outcome measures, designs of the rehabilitation programmes, follow up lengths, or general quality of the trials. Rather, it should be considered whether the null effect are due to the identical comprehensive nature of the rehabilitation programmes being compared in the

RCTs, or whether the complex interplay between individually biopsychosocial factors driving disability in patients with CLBP makes it difficult to improve disability with programmes that more or less have one-size-fits-all approaches (33).

While only the aforementioned single RCT assessed booster sessions in the CLBP and rehabilitation field (48), a review including three RCTs evaluated the effect of booster sessions in addition to exercise therapy in patients with hip and/or knee osteoarthritis. It found moderate evidence for long-term effectiveness with respect to physical function (97). This result is in line with one additional RCT (98), but in contrast to two RCTs (99, 100) in the same field, and as well in contrast to our results. Overall, the evidence base in terms of the effect of adding booster sessions to exercise interventions in the musculoskeletal field remains equivocal.

6.4 Main findings from the process evaluation and their relationship to the main results from the RCT

Overall, the initial analyses of process data provided prospective insight into what we might subsequently find in terms of the overall effect. The findings from changes in referral, administration, and management occurring during the RCT (process research question 2), and the stakeholders' experiences with and perspectives of the integrated programme (process research question 3) are collectively thought to be a drawback of the integrated programme, thereby attenuating any difference between the two rehabilitation programmes.

An exhaustive discussion of all nuances in the process evaluation is not presented, but key examples are given below according to each process research question.

6.4.1 Process research question 1

"Was the integrated programme modified during the trial?"

Allowing for a high degree of flexibility in the delivery of the clinical activities as a part of the pragmatic attitude of the RCT (Table 7 and Figure 5) meant that two major modifications occurred during the RCT. Those were the employment of a psychologist and the change in number of hours and setting of aqua gymnastics, both of which occurred in the integrated and the existing programmes. For this reason, the modifications are not suspected to have influenced the results (108).

Further, the continuous challenge with implementing the exercise capacity test resulted in lack of valid data. Thus, before opening up the data, it was decided to exclude data on exercise capacity from the statistical analyses. In this non-blinded RCT, data on a relative objective outcome such as exercise capacity would have been interesting, as a part of the rehabilitation programme aimed to improve physical outcomes. On the other hand, exercise capacity was not a major component in the

rehabilitation programmes and it may not on its own have revealed a positive effect of successful integration of knowledge, skills and behaviours.

6.4.2 Process research question 2

"What relevant changes to referral, administration, management etc. occurred during the trial?"

The patient-initiated postponements of allocated inpatient stays and the low adherence to the 6-month follow-up visits (despite good overall adherence) is not thought to have a direct effect on the results. However, the effect these events induced amongst the providers, and thus the indirect effect they could have caused, is a cause for concern. This is further discussed in Section 6.4.3.

6.4.3 Process research question 3

"The stakeholders' experiences with and perspectives of the integrated programme"

The changes to referral, administration, and management (Section 6.4.2) spread frustration across the whole setting and could potentially have obstructed the success of the integrated programme by inducing a lack of endorsement for, and belief in, the integrated programme.

The continuous challenges with implementing the pamphlet and the phone calls, which were thought to support integration of knowledge, skills, and behaviours, was rather concerning as it could potentially have served to attenuate any differences between the two rehabilitation programmes.

As these findings emerged, it became obvious that the logistics of implementing the integrated programme in daily clinical practice was a challenge. This could potentially have caused bias in favour of the existing programme, and thereby potentially induce a negative effect on the results.

On reflection, the changes required to implement the integrated programme in daily clinical practice might have been overlooked despite the thorough development and feasibility-testing including PPI; pointing back to the lack of a pilot RCT (Section 6.1.2).

6.4.4 Process research question 4

"The patients' experiences with the integrated programme and with integrating the programme into their daily life"

The patients were interviewed 1 year after the stakeholders, and thus, in general, their experiences did not seem to be affected by the experiences and perspectives of the stakeholders. Thus, the patients' experiences were not thought to be a drawback of the integrated programme.

6.4.5 Process research question 5

"Was the integrated programme delivered as planned?"

Adherence to the inpatient days was excellent, and for that reason, the planned per-protocol analysis was not performed. The lack of adherence, therefore, was not thought to have had an effect on the main results.

6.4.6 Process research question 6

"Did waiting time differ between the two programmes?"

Adjustment for waiting time performed in Studies 2 and 3 did not affect the estimates, thus, waiting time can be rejected to have influenced the main results.

6.5 Strengths and limitations in Studies 2 and 3

When interpreting the results of the RCT, some considerations about the design and the circumstances that occurred during the RCT need elaboration.

The RCT has some strengths according to its design:

- The RCT design is considered the gold standard for studies about effectiveness of interventions, as, if conducted properly, the basic premise is that they minimise known and unknown confounding (109, 110).
- The parallel design, implying that the two rehabilitation programmes were evaluated simultaneously, is expected to ensure that changes in the clinical activities and/or the organisation during the RCT would have an equal impact on the two rehabilitation programmes.
- Stratified randomisation on the basis of baseline disability was performed to achieve approximate balance in mean disability levels and thereby keep this variable equally distributed between the two rehabilitation programmes (79, 108, 109).
- The database that generated the random allocation sequence was set up to use random blocks of six. This allocation concealment prevents selection bias (79, 108-110). Furthermore, the block randomisation ensured that the number of patients could not differ more than three patients between groups (79, 108).
- The PhD candidate performing the statistical analysis was blinded to treatment allocation thereby also preventing bias (31, 79, 108, 109).
- In Study 3, an ITT analysis was performed. This handles bias introduced by missing data by keeping every patient randomised in the RCT, thereby supporting the strengths of the RCT design (108).
- Data were analysed in accordance with pre-specified statistical analysis plans (Appendices 6 and 7) thus, ensuring that the statistical analyses and thus, the results, were not data-driven (111).

Furthermore, some additional strengths in terms of the circumstances that occurred during the RCT need highlighting.

Firstly, patient characteristics were comparable between rehabilitation programmes at baseline. This is vital as a serious imbalance could potentially influence the clinical course and thereby the results (108, 110).

Secondly, patients dropping out from the RCT were similar in numbers and baseline characteristics between groups, hence attrition bias is not suspected (108).

Thirdly, baseline characteristics were comparable between patients lost to follow up and patients who completed the 6-month and 12-month follow up, respectively, thus minimising the risk of selection bias (110).

Fourthly, high adherence to the inpatient days confirmed that the patients actually participated in the rehabilitation programmes (109).

Lastly, the targeted sample size was reached.

This RCT also has a number of limitations which could possibly have distorted the results:

- Theoretically, due to the lack of blinding of patients and providers, knowledge about treatment allocation could have introduced information bias especially in light of all outcome measures being self-reported. Firstly, patients were aware of the comparator programme and the allocation when answering the questionnaires (except from the baseline questionnaire). Secondly, providers were similarly aware and the process evaluation revealed that they compared the two rehabilitation programmes in favour of the existing programme. This could have affected the providers' interaction and communication with the patients. However, since there was no difference between the two rehabilitation programmes either at 6-month or at 12-month follow up, the risk of information bias was not suspected to have biased the results.
- Lack of blinded providers delivering the rehabilitation programmes to non-blinded patients in the same rehabilitation centre, at the same time induced the risk of contamination. This meant that the concept of integration of knowledge, skills, and behaviours could have been transferred to patients in the existing programme by themselves or by the providers. Contamination can dilute any differences between the two rehabilitation programmes, and thereby reduce the point estimate of effectiveness of the integrated programme leading to the risk of a type II error (112). Despite the risk of contamination, the parallel design was

preferred rather than a staggered design where external circumstances could have been different between the rehabilitation programmes (see strengths).

- The degree to which the integration of knowledge, skills, and behaviours led to contamination could potentially have been revealed by measuring adherence to home-based activities, which was not done. Lack of this data precluded us from assessing whether patients in the integrated programme actually integrated the acquired knowledge, skills and behaviours into their daily lives to a higher extent than patients in the existing programme. Thus, we failed to have valuable information to improve our understanding of the mechanisms of treatment failure (108). Measuring adherence to home-based activities is a challenge as there are no obvious good measurement of that domain, it often requires a huge amount of effort from the patients, it can easily be subject to information bias, and it can produce myriad of data.

Internal validity is determined by how well the design, data collection, and analyses are carried out, and can be threatened by bias and confounding (113). Due to their nature, well-conducted RCTs are known to have a strong internal validity as a starting point. When counterbalancing the strengths and limitations according to the design and the circumstances occurring during this RCT, risk of bias and confounding are limited, which supports strong internal validity.

6.6 External validity

A prerequisite for making inferences about external validity, also known as generalisability, is that the internal validity needs to be strong (113). However, there will always be a trade-off between internal and external validity, and thus using a pragmatic attitude maximises external validity but compromises internal validity (32, 105). We attempted to conduct this RCT with a high degree of rigour while also providing strong external validity by applying a pragmatic attitude.

Some aspects with respect to external validity need elaboration. In theory, it could be assumed that those being referred, and those willing to participate differed from the general population of patients with CLBP. Differences in those being referred or differences between those randomised and those declining to participate (n = 71) would affect external validity. We have no reason to suspect differences in referral patterns and there were no differences between those randomised and those declining to participate (n = 71) with respect to baseline characteristics (Section 5.2). These factors along with the broad inclusion- and exclusion criteria, due to the pragmatic attitude of the RCT, support the external validity.

A multicenter study could have enhanced the external validity further as the integrated programme then would have been assessed in various contexts, by different providers, and included a more diverse sample (79). A multicentre study involving all three departments of the rehabilitation centre in Denmark was considered, but unfortunately not possible due to available resources.

7. Conclusion

Firstly, a thorough justification and description of the integrated programme for patients with chronic low back pain was performed.

Secondly, the integrated programme did not lead to improved back-specific disability or other outcomes for patients with chronic low back pain when compared with the existing programme at 6-month follow up.

Thirdly, the integrated programme did not lead to improved back-specific disability or other outcomes for patients with chronic low back pain when compared with the existing programme at 12-month follow up.

8. Implications

This properly planned research process represents the culmination of many decisions, resulting in a successful evaluation of the integrated programme. The dissertation contributed new knowledge about the delivery of multidisciplinary rehabilitation programmes in patients with CLBP. In spite of the null effect, this is still an important finding and some implications deserve consideration.

8.1 For clinical practice

Study 1 succeeded in justifying and describing the integrated programme in detail, allowing for implementation in clinical practice.

The results of Studies 2 and 3 did not provide evidence to support that changing the delivery of a multidisciplinary rehabilitation programme improved the outcome in terms of disability in a population of patients with CLBP after 6 and 12 months. This is useful knowledge in clinical practice where multiple rehabilitation programmes for patients with CLBP exist. Thus, clinicians referring to and clinicians providing, a rehabilitation programme can rightly have doubts about whether a specific rehabilitation programme is effective or not. This dissertation provided an evidence base from which clinicians with their mind at rest can tell their patients that as long as the content stays the same, it is without consequence to change the delivery of the rehabilitation programme. This would induce a positive effect on the patients referred to the rehabilitation programme and for whom it can be necessary to be reassured about the effectiveness of the rehabilitation programme they are referred to and into which they are expected to put a lot of personal effort.

8.2 For research

The thorough description of the integrated programme provided in Study 1 enables other researchers to replicate or build on our research findings. It also enables reviewers to synthesise evidence. Thus, Study 1 is of value for the research community.

While the effect of multidisciplinary rehabilitation in patients with CLBP is well established (7, 22-24), the results from Studies 2 and 3 provided evidence that the two ways of delivering rehabilitation programmes were equal in terms of effect on the chosen outcomes. These results could give rise to a discussion about whether patient preferences should guide the choice of rehabilitation programme. This of course has some implications for clinical practice. Firstly, are the services delivering the rehabilitation programmes able to deliver more than one rehabilitation programme? With this RCT, even though having a highly pragmatic attitude, we experienced some organisational difficulties in delivering more than one rehabilitation programme, at the same time, in the same setting, by the same providers. This implies that the delivery of flexible rehabilitation

programmes may be an enormous challenge in clinical practice requiring huge efforts from the services including the providers delivering the rehabilitation programmes. Many different rehabilitation programmes exist worldwide, but it is questionable if we know enough about what matters to the patients. This could possibly be explored further by qualitative work followed by patient preference clinical trials. However, we need to be aware that patient-preferences are not the only thing, as the context also plays a key role. For example, legislative, social and cultural structures are often different from country to country, and thus, difficult to standardise in clinical practice as well as in research.

In terms of CLBP being driven by biopsychosocial factors, and in light of the plethora of research in the field, it seems like a challenging task to target each individual patient with a primarily one-size-fits-all approach (33). This implies that future research should focus on how to subgroup patients with CLBP to receive more targeted treatment for their complex problems (7, 14, 114).

8.3 For public health

The management of CLBP is vital from a public health perspective both nationally and internationally in light of the burden experienced by the individuals affected, their relatives and society in general. A major weakness of the current RCT and many other RCTs in the same field (7, 44, 103, 104) is the lack of a cost-effectiveness analysis. It is imperative that future research includes cost-effectiveness analyses, as there is an obvious societal interest in achieving the best possible outcome with the least costly rehabilitation programmes.

CLBP should be understood as a condition of life. With the huge amount of available intervention research, new intervention studies are probably not the most optimal solution to stem the challenges facing these patients, their relatives and society. Maybe we need to gain a wider perspective and look into new actions required by the political, public health, and health care systems (21). Firstly, in terms of the political arena, national and international policy-makers ought to increase the public recognition of the effects and burden of low back pain. Secondly, according to the public health challenge, the onset and persistence of disability associated with LBP needs to be prevented. This can be done by changing priorities, systems and practices. Lastly, with respect to the health care system, a shift away from the emphasis on the biomedical and fragmented model of care is required. This implies a change in culture, clinical behaviour, and systems, as well as a need to tackle vested interests.

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10. Appendices

Appendix 1

Study 1

Supplementary file: Appendix 8

Appendix 2

Study 2

Supplementary file 1: Appendix 5

Supplementary file 2: Figure 4 in this dissertation

Appendix 3

Study 3

Supplementary file 1: Appendix 7

Appendix 4

Permission of the UK Medical Research Council to reproduce Figure 1.

Appendix 5

A completed GRIPP2 short form

Appendix 6

Statistical analysis plan – Study 2

Appendix 7

Statistical analysis plan – Study 3

Appendix 8

Activity sheets describing each of the 38 clinical activities

Appendix 9

Graphical depiction comparing the integrated programme and the existing programme

Appendix 10

Examples process research question 1 and 2

Study 1

CLINICAL REHABILITATION

Clinical Rehabilitation
1–9

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The Sano study: justification and detailed description of a multidisciplinary biopsychosocial rehabilitation programme in patients with chronic low back pain

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This series of articles for rehabilitation in practice aims to cover a knowledge element of the rehabilitation medicine curriculum. Nevertheless, they are intended to be of interest to a multidisciplinary audience. The competency addressed in this article is to justify and describe a complex intervention for patients with chronic low back pain before evalutation in a randomised controlled trial.

Abstract

Objective: To justify and describe an integrated rehabilitation programme for patients with chronic low back pain prior to evaluation in a randomized controlled trial.

Method: The Template for Intervention Description and Replication (TIDieR) checklist was used as a structural framework for the description of the integrated rehabilitation programme. As a part of the description, the Medical Research Council guidance, 'Developing and evaluating complex interventions', was used as a framework to justify the integrated rehabilitation programme.

Intervention description: The integrated rehabilitation programme adopts a participatory biopsychosocial approach integrating inpatient activities supported by a multidisciplinary team and learning located within the patient's own environment. The integrated rehabilitation programme comprises 3 weeks of inpatient stay and 11 weeks of home-based activities. The inpatient part of the programme consists of 38 clinical activities, some of them delivered more than once. The 38 clinical

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activities were described in an activity sheet developed for this purpose, combining five items from the TIDieR.

Conclusion: An integrated rehabilitation programme for patients with chronic low back pain has been justified and described. The intervention description is currently being used for successful structuring and standardization of the content and delivery of the integrated rehabilitation programme in a randomized controlled trial.

Trail registration: ClinicalTrials.gov: NCT02884466.

Keywords

Chronic low back pain, complex interventions, biopsychosocial model, TIDieR, medical research council (MRC) guidance

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Introduction

Besides pain and disability, patients with chronic low back pain often experience psychosocial consequences affecting their social, leisure and work life.[1–3] Recognition of the biopsychosocial consequences of disease in general[4,5] led to the development of the biopsychosocial model.[1,6–8] In multidisciplinary rehabilitation,[7,9] where the consequences of disability are managed,[7] the biopsychosocial model is widely accepted. Multidisciplinary rehabilitation of patients with chronic low back pain is considered a complex intervention carried out in a complex environment.[10,11] Evaluation of complex interventions in randomized controlled trials is a major research area. Detailed published descriptions of interventions are needed as it enables implementation of the intervention into a real-life setting,[12–14] it enables other researchers to replicate or build on research findings[13,14] and it further enables reviewers to synthesize extant evidence.[14,15] The Template for Intervention Description and Replication (TIDieR) checklist was developed to improve this issue.[13]

We developed an integrated rehabilitation programme adopting a participatory biopsychosocial approach and integrating inpatient activities supported by a multidisciplinary team and learning located in the patient's own environment. The aim of this article is to justify and describe the integrated rehabilitation programme in detail prior to a randomized controlled trial (ClinicalTrials.gov: NCT02884466).

Intervention description

The TIDieR checklist[13] was used to structure the detailed description of the integrated rehabilitation programme.

Item 1. Brief name

An integrated rehabilitation programme alternating between inpatient stays and home-based activities in patients with chronic low back pain.

Item 2. Why: describe rational and theory essential to the intervention

The integrated rehabilitation programme was justified using a systematic iterative model developed by the British Medical Research Council for developing and evaluating complex interventions.[16,17] Patients, providers, administrators and managers were continuously involved[18] in the development and piloting stages. The development stage consists of three steps: (1) identifying the evidence base, (2) identifying/developing theory and (3) modelling process and outcomes.[16,17]

In the first step, 55 randomized controlled trials were identified as the existing evidence base. In total, 53 studies were included in a Cochrane

review on multidisciplinary biopsychosocial rehabilitation for chronic low back pain.[1] The Cochrane review found rehabilitation to be more effective than usual care (moderate quality evidence) and physical treatments (low quality evidence) in reducing long-term pain and disability in patients with chronic low back pain.[1] The effect for pain and disability were generally larger in the short and medium term than in the long term.[1] An updated literature search identical to the Cochrane review[1] was performed, and further two studies were included in the evidence base;[19,20] this did not alter the conclusion of the Cochrane review.[1] In total, 5 of the 55 studies[20–24] assessed a rehabilitation programme with subsequent booster sessions. Two of the five studies[21,22] assessed an inpatient rehabilitation programme with booster sessions; of these, only one study compared two inpatient rehabilitation programmes, one of which included booster sessions.[22] This study[22] compared a three-week orthopaedic inpatient rehabilitation programme with two four-week multidisciplinary inpatient rehabilitation programmes, one of which included seven subsequent telephone booster sessions. Significant advantages in favour of the multidisciplinary programmes were found on pain coping strategies. However, no difference was found on disability or between the two multidisciplinary programmes.[22]

In the second step, the theoretic foundation of the integrated rehabilitation programme was based on a biopsychosocial rehabilitation model and approach[7,11,25,26] and the Chronic Care Model.[27–30] Following the development of the biopsychosocial model, multidisciplinary rehabilitation programmes that target the biopsychosocial aspects of chronic low back pain have been widely discussed and partly implemented.[1,31] The International Classification of Functioning, Disability and Health (ICF)[26] addresses the dimensions of disability[9,26] and offers a framework for applying the biopsychosocial model to clinical practice, especially to multidisciplinary rehabilitation.[7,9] An important aspect in biopsychosocial rehabilitation is the time the patients spend practicing and learning which assigns the patients a central role in managing their own health.[7,25] Most activities are directly influenced by the context, and any process aiming at optimizing functioning must therefore take the patient's environment into account.[7] Thus, patients undergoing rehabilitation should practice in the environment in which the activity takes place; this will mainly be in everyday life situations and contexts rather than in institutions. A multidisciplinary team can effectively manage the complex problems with regard to functioning and disability by assisting practicing and learning through expert assessment, identification of self-directed goals, advice regarding a suitable plan, teaching encouragement and providing feedback.[7,11,25]

The mind-set described above is concurrent with essential elements in the Chronic Care Model, developed to guide and encourage high-quality chronic care for a variety of chronic illnesses, healthcare settings and target populations.[27] The Chronic Care Model pays attention to patient self-management and self-management support from skilled providers.[27] Due to the long-time horizon and fluctuating course of most chronic diseases, regular interaction between patients and providers is required.[27] Therefore, the Chronic Care Model emphasizes the importance of regularly scheduled booster sessions in order to assess response to therapy and self-management skills and adjust treatment,[27] and in order to obtain information on functional status, identify potential barriers, check progress and reinforce patient efforts.[28] Booster sessions are described to improve patient outcome and can be accomplished by, for example, scheduled return visits, telephone calls or emails.[28,29] It is suggested that a context outside the traditional healthcare setting (e.g. the patients' home) is more effective in the care of chronic diseases.[30]

In the third step, the processes and outcomes were modelled as recommended.[32] As a result, the clinical activities were grouped into 10 key components delivered by the multidisciplinary team (see Table 1).

The 38 clinical activities from an existing rehabilitation programme were reorganized into the integrated rehabilitation programme. Thus, the clinical activities in the two programmes are identical; however, the two programmes differ in mode of delivery, with the existing rehabilitation programme being a 4-week inpatient programme and the integrated

Table 1. The 10 key components and the 38 clinical activities.

Key component	Clinical activity
Clinical assessment	Physical assessment
	Psychosocial assessment
Motivation and change	Instruction in exercise app
	Introduction to rehabilitation
	Exercise theory
	Introduction to mindfulness
	Involvement of relatives
	Motivation and anchoring
	The next step
Pain knowledge and management	Chronic pain and chronic back pain
	Experiences with pain
	Knowledge about pain
	Knowledge about analgesic medicine
	Living with pain
Multidisciplinary intervention	Welcome meeting
	Multidisciplinary conference
	Open counselling
	Midterm evaluation
Exercise and physical activity	Aqua gymnastic
	Circuit training
	Intro electric bicycle
	Exercise capacity training
	Healthy feet
	Closing activity
Individual counselling	Individual nurse counselling
	Individual physiotherapy counselling
	Individual occupational therapy counselling
	Individual dietary counselling
	Individual rheumatological counselling
Essential activity	Activity and health
	Balanced activity
	Activity and social relations
	Lifelong activity
Activities of daily living	Sleep
	House and garden
Nutrition and weight loss	Permanent weight loss strategies
	Healthy lifestyle
Individual exercise	Individual exercise

rehabilitation programme being a 14-week programme alternating between in total 3 weeks of inpatient activities and 11 weeks of home-based activities (see Figure 1). The two programmes will be compared in a randomized controlled trial.

To summarize the development stage: despite a large body of literature on multidisciplinary biopsychosocial rehabilitation and chronic low back pain, there is a lack of evidence supporting how to maintain the best long-term effect of a rehabilitation programme. Furthermore, evidence regarding the effectiveness of continuous integration of learning into the patient's own environment underpinned and aided by inpatient booster sessions delivered by a multidisciplinary team is lacking. Based on the evidence base and the identified

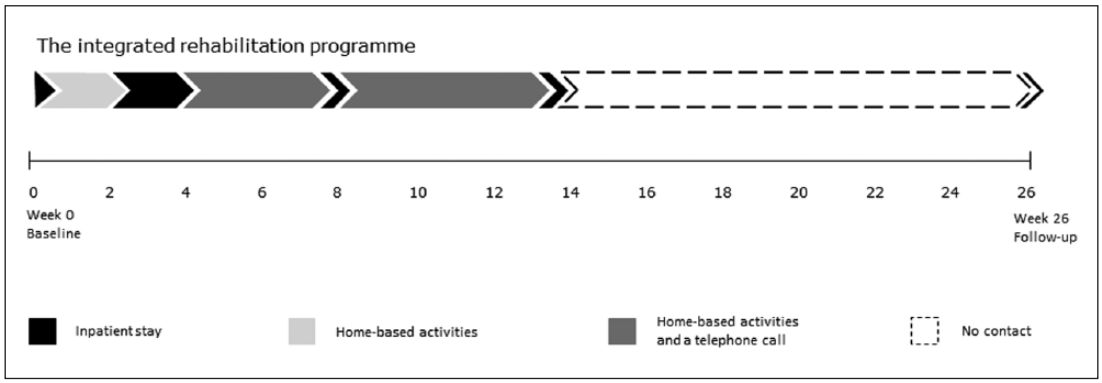

Figure 1. The integrated rehabilitation programme consists of (1) a pre-admission day, (2) 2 weeks of home-based activities, (3) 2 weeks of inpatient programme, (4) 4 weeks of home-based activities, (5) two days of inpatient programme, (6) 6 weeks of home-based activities, (7) two days of inpatient programme and (8) 26-week follow-up.

theoretic foundation,[7,11,25–30] we assumed that a rehabilitation programme integrating inpatient stays supported by a multidisciplinary team and home-based activities would allow for a high degree of learning. When at home, the patients will be able to integrate what they have learned while being inpatient into activities and participation in interaction with their everyday life situations and environment. When inpatient, the patients' experiences from home will be integrated in the inpatient rehabilitation process supported by a multidisciplinary team. We hypothesized this integration of inpatient stays, and home-based activities would improve rehabilitation efforts and optimize long-term effect. The hypothesis was in accordance with clinical experiences and requests from patients, providers, administrators and managers.

The piloting stage consists of three steps: (1) testing procedures, (2) estimating recruitment/retention and (3) determining sample size.[16,17] In the first step, the procedures were tested. This lead to fine-tuning of administrative and practical procedures, for example, permanent overbooking each week as two to three patients in every group postponed their appointments.

In the second step, recruitment/retention was estimated deeming the number of eligible patients, and the intended willingness to participate was large enough to recruit a sufficient number of patients. In the third step, sample size was estimated resulting in a planned recruitment of 160 patients. Altogether, information obtained from the development and piloting stages comprised the rationale justifying the evaluation of the integrated rehabilitation programme.

Item 3. What (materials)

The facilities include classrooms, learning labs (e.g. a fully equipped kitchen), conversation rooms, a small hot water pool and indoor and outdoor fitness facilities with cardio exercise equipment and strength training equipment.

A welcome pamphlet describing the clinical activities and a pamphlet containing individualized preparation material focusing on facilitation of goal setting as well as physical and mental preparation before the next inpatient stay are provided.

Item 4. What (procedures)

The 38 clinical activities addressing different components in the ICF model were grouped into 10 key components (Table 1). Activity sheets describing the clinical activities are provided as a supplemental file. See Table 2 for an example of an activity sheet.

Table 2. Example of an activity sheet developed to describe the clinical activities.

What (procedures)		Aqua gymnastic Aerobe and anaerobe exercises as well as exercises focusing on mobility and stability/balance
Tailoring		The exercises are chosen and adjusted based on the individual patient
Who provided		Physiotherapist
How		Group session
When and how much	Number of sessions	Supervised: four sessions Non-supervised: six sessions
	Duration	30 minutes including warm-up and cool-down
	Intensity	Borg 11–15

Item 5. Who provided

The multidisciplinary team consists of a rheumatologist, a nutritional counsellor, three nurses, three occupational therapists and six physiotherapists. The majority of the providers are trained in motivational interviewing. Other employees are administrative assistants, night-shift nurses, groundsmen, a chef, a cleaner and a daily manager, all in close contact with the patients. All providers have the required skills in delivering the clinical activities. See supplemental file for further details.

Item 6. How: modes of delivery

Patients will be contacted by phone at the time of visitation and four weeks before the pre-admission day. In addition, the welcome pamphlet (see item 3) will be emailed to the patients at this point. The integrated rehabilitation programme is delivered as a combination of theory and practice consisting of individual counselling, group sessions and lectures. Sessions are delivered face-to-face except for the non-supervised exercise. In order to assure support for the patients between the inpatient stays, a pamphlet (see item 3) and telephone calls once during each of the last two home periods (see Figure 1) will be used. Furthermore, patients are allowed to contact the providers online twice until the end of the 14-week programme. See supplemental file for further details.

Item 7. Where: type of location

The department under study is the Danish Rheumatism Association's highly specialized multidisciplinary rehabilitation centre Sano Aarhus. Patients are referred from both rural and urban areas of Denmark based on a rheumatic or musculoskeletal disease and their ability and motivation to participate in a rehabilitation programme. The programme is tax-financed. A new group of six to eight patients is admitted each week, which means that approximately 28 patients divided between four groups are inpatient at the same time.

Item 8. When and how much

During the inpatient stays, 38 clinical activities are provided, some of them more than once. See supplemental file for further details.

Item 9. Tailoring

The integrated rehabilitation programme is partly standardized and partly patient-centred. Patient-centred rehabilitation requires tailoring of the programme to the individual patient. Tailoring occurs (1) during the multidisciplinary conference including the identification of self-directed goals,[33] (2) in the individual counselling and (3) in the exercise and physical activity sessions. Therefore, what the patients actually receive differs as a result of tailoring the intervention to individual needs. See Table 1 and the supplemental file for further details.

Item 10. Modifications during the course of the study

An ongoing process evaluation[34] is conducted in order to register modifications during the full-scale randomized controlled trial. Modifications will be reported in the evaluation study.

Item 11. How well (planned)

Attendance to inpatient stays, time between the inpatient stays and attendance to the clinical activities during inpatient stays are registered in each individual patient's electronic health record.

Item 12. How well (actual)

Attendance will be reported in the evaluation study.

Discussion

An integrated rehabilitation programme for patients with chronic low back pain has been developed and described using the TIDieR. In order to justify the integrated rehabilitation programme, we embarked on a development and piloting process in accordance with the Medical Research Council guidelines.[17] Identical to previous descriptions of complex interventions,[35–37] we experienced difficulties integrating information from the development and piloting stage into the TIDieR framework. Therefore, a description of the development and piloting process was included in item 2 in order to provide evidence supporting and justifying the integrated rehabilitation programme. A transparent development and piloting process may lead to a better understanding of the possible mechanisms and effects of a rehabilitation programme.

The TIDieR was useful in providing a structured framework offering an opportunity to describe in detail the main characteristic of each of the 38 clinical activities comprising the integrated rehabilitation programme. In order to structure and standardize the description of the clinical activities, we developed an activity sheet. The activity sheet combines 'What (procedures)', 'Who provided', 'How', 'When (and how much)' and 'Tailoring' from the TIDieR. It is reasonable to use the activity sheet as the TIDieR does not reflect the order in which information should be presented.[13] The Consensus on Exercise Reporting Template (CERT)[12] is a valuable adjunct to or extension of the TIDieR when describing exercise interventions. For consistency, the CERT has harmonized its domains and the order of items with the TIDieR. In addition to the TIDieR, the CERT integrates precise information about the type of exercise, dosage, intensity, frequency and supervision/individualization.[12] Inspired by the CERT, we incorporated the precise information needed for exercise interventions in the activity sheet.

The integrated rehabilitation programme is designed to integrate inpatient learning into the everyday life of patients with chronic low back pain. The strengths of the integrated rehabilitation programme are as follows. First is the adoption of a systematic and transparent approach using the Medical Research Council guidelines;[16] this process ensured the overall approach of the integrated rehabilitation programme and proceeding to a full-scale study was justified. Second, the detailed description as recommended for complex interventions ensured implementation into a real-life clinical setting and replication in other contexts following the evaluation. Third, patients, providers, administrators and managers were continuously involved in the development, piloting and detailed description of the integrated rehabilitation programme, thereby ensuring commitment, broad support, engagement and ownership from all persons involved in the study.

Due to the complexity of the integrated rehabilitation programme it is difficult if not impossible to synthesis and justify the evidence supporting each of the 38 clinical activities.

It is a premise that a complete, detailed description of a complex intervention, that consists of multiple clinical activities, involves a multidisciplinary team, is partly tailored and is sensitive to the context, is impossible. The integrated rehabilitation programme was described to a level of detail that was found adequate, as the main function of the intervention is now clearly described.

The development, piloting and description of the Sano study was iterative and time-consuming, but necessary when aiming to minimise the risk that the research project would be a waste of time or unetichal or both. We cannot reject that the integrated rehabilitation programme could be identical to earlier rehabilitation programmes assessed in randomized controlled trials as most of the earlier studies lack detailed descriptions of their rehabilitation programme. The intervention description is currently being used for successful structuring and standardization of the content and delivery of the integrated rehabilitation programme in a randomized controlled trial.

Clinical Messages

- An integrated rehabilitation programme integrating learning into the patient's environment was justified and described in detail.
- The Template for Intervention Description and Replication (TIDieR) checklist provided helpful recommendations for the reporting of a multidisciplinary rehabilitation programme.
- An activity sheet combining five items from the TIDieR checklist and presenting the clinical activities was developed.

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Study 2

Original Article

CLINICAL REHABILITATION

Clinical Rehabilitation
1–12

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The effect of an integrated multidisciplinary rehabilitation programme alternating inpatient interventions with home-based activities for patients with chronic low back pain: a randomized controlled trial

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Abstract

Objective: To compare the effectiveness of an integrated rehabilitation programme with an existing rehabilitation programme in patients with chronic low back pain.

Design: A single-centre, pragmatic, two-arm parallel, randomized controlled trial (1:1 ratio).

Setting: A rheumatology inpatient rehabilitation centre in Denmark.

Subjects: A total of 165 adults (aged ⩾ 18 years) with chronic low back pain.

Interventions: An integrated rehabilitation programme comprising an alternation of three weeks of inpatient stay and 12 weeks of home-based activities was compared with an existing rehabilitation programme of four weeks of inpatient stay.

Main measures: Patient-reported outcomes were collected at baseline and at the 26-week follow-up. The primary outcome was back-specific disability (Oswestry Disability Index). Secondary outcomes included pain intensity (Numerical Rating Scale), pain self-efficacy (Pain Self-Efficacy Questionnaire), health-related quality of life (EuroQol-5 Domain 5-level (EQ-5D)), and depression (Major Depression Inventory). A complete case analysis was performed.

Results: A total of 303 patients were assessed for eligibility of whom 165 (mean age: 50 years (SD 13) and mean Oswestry Disability Index score 42 (SD 11)) were randomized (83 to existing rehabilitation

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programme and 82 to integrated rehabilitation programme). Overall, 139 patients provided the 26-week follow-up data. Baseline demographic and clinical characteristics were comparable between programmes. The between-group difference in the Oswestry Disability Index score when adjusting for the corresponding baseline score was −0.28 (95% confidence interval (CI): −4.02, 3.45) which was neither statistically nor clinically significant. No significant differences were found in the secondary outcomes.
Conclusion: An integrated rehabilitation programme was no more effective than an existing rehabilitation programme at the 26-week follow-up.

Keywords
Chronic low back pain, multidisciplinary rehabilitation, biopsychosocial approach, complex interventions

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Introduction

Multidisciplinary rehabilitation is recommended as a second-line treatment for patients with chronic low back pain who do not respond to first-line treatments.[1,2] 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 approach.[1–4] There are different ways of delivering multidisciplinary rehabilitation. A Cochrane review included 12 randomized controlled trials comparing at least two different multidisciplinary rehabilitation approaches,[3] 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 known.[3]

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 account[5,6] and ensuring regular interaction over time between the patient and the multidisciplinary team via scheduled booster sessions.[7] One trial included in the Cochrane review[3] assessed the effect of adding booster sessions (phone calls) to a four-week inpatient rehabilitation programme.[8] The trial found a small, but not statistically significant, benefit compared with the same inpatient rehabilitation programme without booster sessions.[8]

From a theoretical point of view, it seems reasonable to combine the biopsychosocial approach[5,9] with the Chronic Care Model[7] in terms of supporting integration of knowledge, skills, and behaviours gained from an inpatient rehabilitation programme into the patient's own environment and daily life.[10]

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 two-week inpatient stay, followed by home-based activities plus two further inpatient booster sessions (each lasting two days).[10] We hypothesized 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 Statement.[11]

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 (Supplemental Material 1). A process evaluation was integrated into the trial as advocated for complex interventions[13] (Supplemental Material 2).

This was a single-centre, pragmatic, two-arm parallel randomized controlled trial conducted in a rheumatology rehabilitation centre in Aarhus, Denmark.[10] Patients were referred to the rehabilitation centre where the trial was conducted from general practitioners or hospital departments.[10] The rheumatologist at that centre identified potentially eligible patients based on the clinical problem detailed on the referral request and a list of International Classification of Diseases, 10th revision (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 emailed 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 the rheumatologist 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 $\geqslant 3$),[14] (2) a diagnosis of axial spondyloarthritis, (3) spinal fracture within the last three 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 <21).[15]

A computer-generated randomization with 1:1 allocation in random blocks of six ensuring allocation concealment was performed by the research assistant. Randomization was stratified on the basis of disability at baseline using the Oswestry Disability Index score with cutoff at 41[15] 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 recommendations.[1,2] The researcher who performed the statistical analysis was blinded.

A secure electronic database was used to email questionnaires and store data. Patients were emailed the questionnaires 10 days prior to the inpatient stay. A reminder was emailed after five and eight 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.

Data on sex, age, marital status, smoking, leg pain, employment status and education level were collected at baseline. The outcome measures were collected (1) before randomization (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).

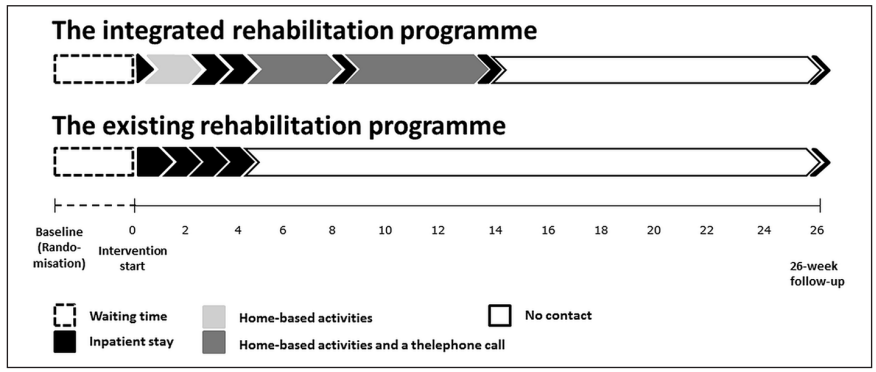

Figure 1. The integrated programme and the existing programme being compared.

The choice of outcome domains and outcome measures was based on patient and public involvement in combination with international recommendations.[16–18] The primary outcome was back-specific disability assessed by the Oswestry Disability Index version 2.1a.[15] Secondary outcomes were back pain intensity assessed by a Numerical Rating Scale,[18] pain self-efficacy measured by the Pain Self-Efficacy Questionnaire,[19] health-related quality of life measured by the EuroQol-5 Domain 5-level (EQ-5D 5L),[20] depression measured by the Major Depression Inventory,[21] and physical activity assessed by three questions.[22]

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 previously.[10] 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) preadmission day, (2) two-week home-based activities, (3) two-week inpatient stay, (4) four-week home-based activities, (5) first two-day inpatient booster session, (6) six-week home-based activities, (7) second two-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 interventions[13] as previously described.[10]

Patients in the existing programme were offered a four-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.

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 difference.[15] The trial was powered to be able to detect a standardized

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 a feasibility test 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 summarized and presented as the mean (SD) or number (%) according to patients allocated at baseline and patients providing 26-week follow-up. In addition, differences in sex, age, and ICD-10 diagnosis codes are presented for those patients randomized and those declining to participate.

The primary analysis 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 randomization (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 $\leqslant 0.05$ were considered statistically significant. For statistical analysis, STATA, versoin 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 $\geqslant 80\%$) was excellent in both arms of the trial (100% in the existing programme and 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.

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.

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

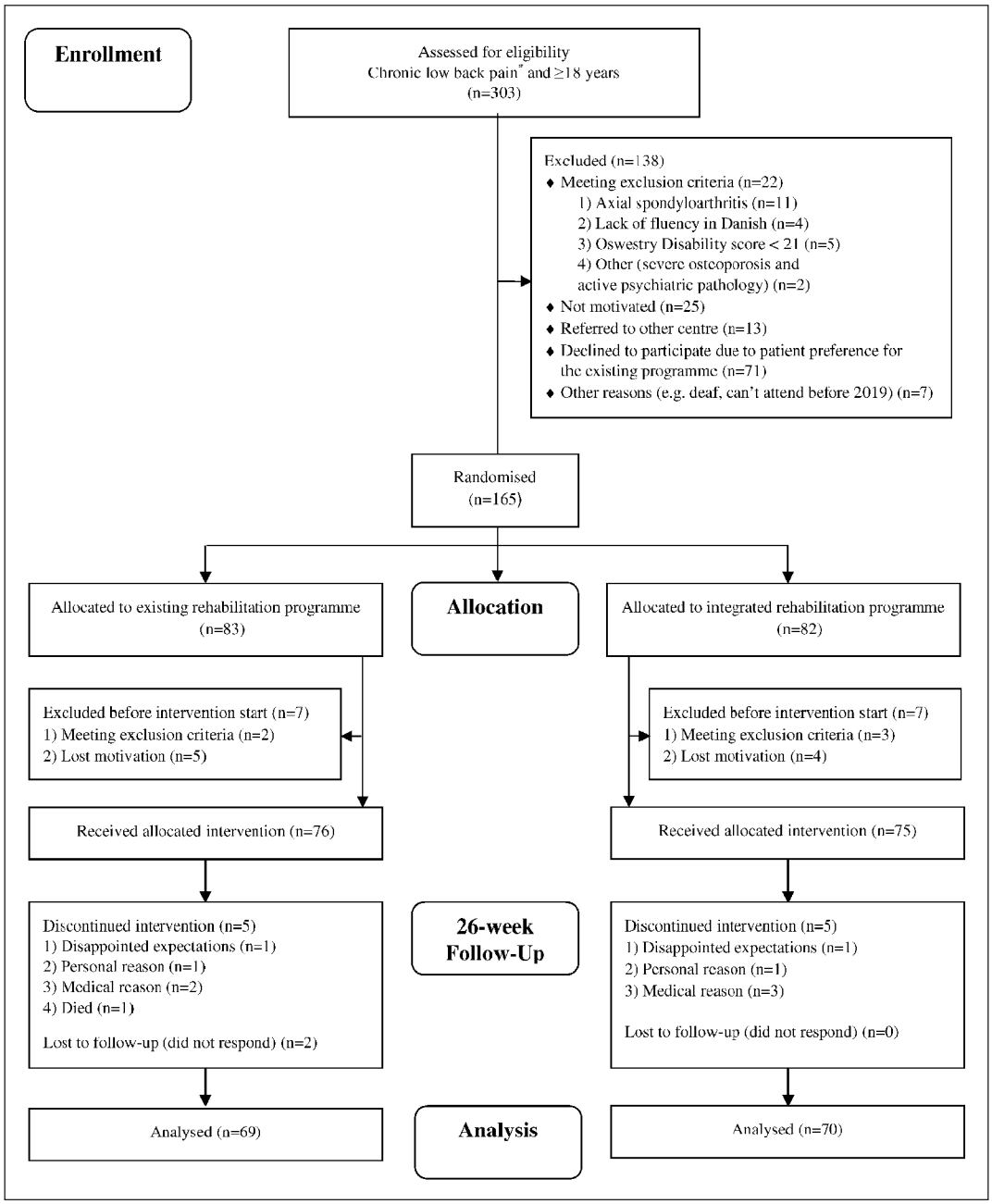

Figure 2. Flow-chart of participants through the trial.
*The following ICD-10 diagnosis codes for diseases, signs, and symptoms related to chronic low back pain were used: DM40, DM41, DM42, DM43 (not 43.3, 43.4, 43.6), DM47, DM48, DM51, DM53 (not 53.0, 53.1), DM54 (not 54.0, 54.2, 54.6), DM96.1, and DT91.0.

Table 1. Characteristics of the population at baseline.

	Patients allocated at baseline		Patients providing 26-week follow-up data	
	Existing programme, $n = 83$	Integrated programme, $n = 82$	Existing programme, $n = 69$	Integrated programme, $n = 70$
Sex (women), *n* (%)	60 (73)	60 (72)	49 (71)	52 (74)
Age (years)				
Mean (SD)	51 (13)	49 (13)	52 (12)	50 (12)
Range	25–84	22–72	25–84	28–72
Marital status, *n* (%)				
Married	58 (70)	60 (73)	50 (72)	51 (73)
Single/widowed	25 (30)	22 (27)	19 (28)	19 (27)
Smokers, *n* (%)				
Yes	28 (34)	24 (29)	23 (33)	17 (24)
No	55 (66)	58 (71)	46 (67)	62 (76)
Leg pain, *n* (%)				
Yes	59 (71)	65 (79)	49 (71)	55 (79)
No	17 (21)	12 (15)	14 (20)	12 (17)
Do not know	7 (8)	5 (6)	6 (9)	3 (4)
Employment status[a], *n* (%)				
Self-supporting	16 (25)	17 (26)	15 (29)	17 (30)
Temporary social benefits	11 (17)	9 (14)	8 (15)	7 (13)
Permanent social benefits	27 (42)	29 (45)	20 (39)	24 (43)
Age-related pension	10 (16)	8 (12)	9 (17)	7 (13)
Others	0 (0)	2 (3)	0 (0)	1 (2)
Education level[a], *n* (%)				
Low (⩽12 years)	14 (22)	10 (15)	11 (21)	6 (11)
Middle (⩽16 years)	44 (69)	44 (68)	36 (69)	40 (71)
High (>16 years)	6 (9)	11 (17)	5 (10)	10 (18)
Disability[b] ODI (0–100)				
Mean (SD)	43 (11)	42 (10)	43 (12)	41 (11)
Range	24–72	20–68	24–72	20–68
Back pain intensity[c] NRS (0–10)				
Mean (SD)	6 (2)	6 (2)	6 (2)	6 (2)

(Continued)

Table 1. (Continued)

	Patients allocated at baseline		Patients providing 26-week follow-up data	
	Existing programme, $n = 83$	Integrated programme, $n = 82$	Existing programme, $n = 69$	Integrated programme, $n = 70$
Pain Self-efficacy PSEQ (0–60)				
Mean (SD)	27 (10)	28 (11)	27 (11)	28 (12)
Quality of life EQ-5D 5L (–0.624 to 1)				
Mean (SD)	0.603 (0.118)	0.567 (0.157)	0.599 (0.126)	0.578 (0.153)
Depression MDI (0–50)				
Mean (SD)	20 (11)	20 (12)	22 (11)	19 (11)
Physical activity, *n* (%)				
Minutes spent on physical exercise during a week				
<30	50 (60)	42 (51)	41 (59)	34 (49)
$\geqslant 30 \leqslant 120$	31 (37)	32 (39)	26 (38)	28 (40)
>120	2 (3)	8 (10)	2 (3)	8 (11)
Minutes spent on physical activity during a week, *n* (%)				
<30	20 (24)	13 (16)	17 (25)	9 (13)
$\geqslant 30 \leqslant 300$	55 (66)	52 (63)	45 (65)	45 (64)
>300	8 (10)	17 (21)	7 (10)	16 (23)
Hours spent sitting during 24 hours, *n* (%)				
$\geqslant 10$	14 (17)	9 (11)	6 (9)	7 (10)
$<10 \geqslant 4$	52 (63)	53 (65)	51 (74)	47 (67)
<4	17 (20)	20 (24)	12 (17)	16 (23)

Columns 1 and 2 show patients randomized ($n = 165$) and columns 3 and 4 show patients providing 26-week follow-up data ($n = 139$).
ODI: Oswestry Disability Index; NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; EQ-5D 5L: EuroQol-5 Domain 5-level; MDI: Major Depression Inventory.
[a]Due to technical issues in the database, data on employment status and education level was only available in ≈75% of the patients.
[b]Due to technical issues in the database, one patient with an ODI score of 20 was included.
[c]Mean back pain intensity for the last two weeks.

Table 2. Summary of 26-week follow-up data on primary and secondary outcomes: between-group and within-group change – complete case analysis.

	Between-group[a]		Within-group	
	Mean (95% CI)	*P*-value	Existing programme (*n* = 69)	Integrated programme (*n* = 70)
			Mean (95% CI)	Mean (95% CI)
Primary outcome				
Disability (ODI)	−0.28 (−4.02, 3.45)	0.881	−5.64 (−8.45, −2.83)	−5.76 (−8.31, −3.20)
Secondary outcomes				
Pain intensity[b] (NRS)	−0.02 (−0.64, 0.59)	0.937	−0.64 (−1.08, −0.19)	−0.76 (−1.21, −0.31)
Pain Self-Efficacy (PSEQ)	0.05 (−3.47, 3.57)	0.978	6.22 (3.63, 8.80)	6.01 (3.48, 8.80)
Quality of life (EQ-5D 5L)	0.01 (−0.03, 0.05)	0.670	0.03 (0.00, 0.07)	0.05 (0.02, 0.08)
Depression (MDI)	0.62 (−1.98, 3.21)	0.639	−4.57 (−6.52, −2.62)	−3.3 (−5.27, −1.24)

CI: confidence interval; ODI: Oswestry Disability Index; NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; EQ-5D 5L: EuroQol-5 Domain 5-level; MDI: Major Depression Inventory.
[a]Adjusted for corresponding baseline value. Existing programme as reference group.
[b]Mean pain intensity for the last two weeks.

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 guidelines,12 and systematic review evidence,[3] 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 session.[10] 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 pain.[16–18] On the contrary, 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 trials[23–25] in addition to the 12 trials already included in the most recent Cochrane review[3] that compared two or more multidisciplinary rehabilitation programmes. Of all 15 trials identified, only two used the Oswestry Disability Index as their primary outcome measure.[24,25] The changes they observed in back-specific disability are similar to those we observed with a within-group decrease of between 7 and 9 points at the 12-week follow-up[24] and a within-group decrease between 2 and 5 points at the 52-week follow-up.[25] Neither of these trials found significant between-group differences,[24,25] 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 benefit.[8] A review including three trials[26] and a further single trial[27] 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 osteoarthritis.[28,29] These conflicting results question the effectiveness of adding booster sessions.

The strengths of this trial include the randomized 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 interventions,[13] including patient and public involvement (Supplemental Material 1) as well as the integrated process evaluation (Supplemental Material 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 article. 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 messages

- 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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Author contributions

All authors have contributed substantially to (1) conception and design, or analysis and interpretation of data; (2) drafting or revising the article critically for important intellectual content; and (3) final approval of the version to be published.

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Supplemental material

Supplemental material for this article is available online.

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Study 3

Clinical Rehabilitation

The effect of an integrated multidisciplinary rehabilitation programme for patients with chronic low back pain: long-term follow up of a randomised controlled trial.

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Keywords:	Chronic low back pain, multidisciplinary rehabilitation, biopsychosocial approach, complex interventions

Abstract

Objective: To compare the long-term effectiveness of an integrated rehabilitation programme with an existing rehabilitation programme, in terms of back-specific disability, in patients with CLBP.

Design: A single-centre, pragmatic, two-arm parallel, randomised controlled trial.

Setting: A rheumatology rehabilitation centre in Denmark.

Subjects: A total of 165 adults (aged ≥ 18 years) with chronic low back pain.

Interventions: An integrated programme (a pre-admission day, 2 weeks at home, 2 weeks inpatient followed by home-based activities, plus two 2-day inpatient booster sessions, and 6-month follow-up visit) was compared with an existing programme (4-week inpatient, and 6-month follow-up visit).

Main measure: The primary outcome was disability measured using the Oswestry Disability Index after 1 year. Secondary outcomes included pain intensity (Numerical Rating Scale), pain self-efficacy (Pain Self-Efficacy Questionnaire), health-related quality of life (EuroQol-5 Domain 5-level (EQ-5D)), and depression (Major Depression Inventory). Analysis was by intention-to-treat, using linear mixed models.

Results: 303 patients were assessed for eligibility of whom 165 patients (mean age 50 years (SD 13) with a mean Oswestry Disability Index score of 42 (SD 11)) were randomly allocated (1:1 ratio) to the integrated programme (n = 82) or the existing programme (n = 83). The mean difference (integrated programme minus existing programme) in disability was -0.53 (95% CI -4.08 to 3.02); p = 0.770). No statistically significant differences were found in the secondary outcomes.

Conclusion: The integrated programme was not more effective in reducing long-term disability in patients with chronic low back pain than the existing programme.

Introduction

Multidisciplinary rehabilitation is recommended as second-line treatment in the management of chronic low back pain (1-3). It is based on the widely accepted biopsychosocial approach (1, 4, 5) and comprises a multifaceted intervention targeting the wide range of modifiable factors known to contribute to chronic low back pain (6). The team providing rehabilitation can reinforce integration of knowledge, skills and behaviours by taking the patient's environment into account (5, 7) and ensuring regular interaction with the patient via scheduled booster sessions (8). However, the optimal dose, content and delivery of multidisciplinary rehabilitation programmes remain unknown (4).

Therefore, as described in a previous paper, we designed an integrated multidisciplinary rehabilitation programme comprising inpatient stays alternating with home-based activities and booster sessions (9). The intention was to support integration of new knowledge, skills and behaviours gained from a multidisciplinary inpatient rehabilitation programme into the daily life of patients with chronic low back pain (9). In another previous paper, we reported results from the 6-month follow up from a randomised controlled trial comparing an integrated rehabilitation programme with an existing rehabilitation programme (10).

Long-term (1 year) follow-up data on the effect of such a rehabilitation programme are needed given that time is thought to be related to successful integration of new knowledge, skills, and behaviours (11). Consequently, the aim of this paper was to compare the effectiveness of the integrated programme with an existing programme in terms of back-specific disability in patients with chronic low back pain at 1-year follow up.

Methods

This was a single-centre, pragmatic, two-arm parallel, randomised controlled trial comparing two rehabilitation programmes for patients with chronic low back pain (9, 10). The clinical activities comprising the rehabilitation programmes have been described (9) and adhere to the Template for Intervention Description and Replication (TIDieR) checklist (12). The participants, randomization procedures, outcomes, and sample size have been described in detail in the 6-month follow-up paper (10) and adhere to Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement (13).

The key difference between the two rehabilitation programmes being compared was the way in which they were delivered (Figure 1).

The differences and similarities between the two rehabilitation programmes are illustrated in Table 1.

[Insert Table 1]

Baseline characteristics were collected before randomisation (t0). Outcome measures were collected several times. Measurement time points in both groups were identical at baseline (t0), before intervention start (t1), before the 6-month follow-up visit (t7), and 1 year after the start of the rehabilitation programme (t8) (Figure 1).

[Insert Figure 1]

The choice of outcome domains and outcome measures was based on patient and public involvement (10) in combination with international recommendations (14, 15). The primary outcome was back-specific disability, assessed by the Oswestry Disability Index version 2.1a (16). Secondary outcome measures were back pain intensity assessed by a Numerical Rating Scale (14), pain self-efficacy measured by the Pain Self-Efficacy Questionnaire (17), health-related quality of life measured by the EQ-5D 5L© (18) and depression measured by the Major Depression Inventory (19).

Descriptive statistics were presented with means and standard deviations (SD) or numbers and percentages, depending on the type of variable. The primary analysis was performed as an intention-to-treat analysis including the four identical measurement time points (t0, t1, t7 and t8). Intervention effects on the primary and secondary outcomes were estimated by the difference in change between the two groups (integrated programme minus existing programme) from baseline to 1 year using a linear mixed model with a random intercept. The analysis included time (as a categorical variable), group, and the interaction between group and time as the only explanatory variables. Furthermore, the linear mixed model was used to test if the outcomes over time in the two rehabilitation programmes were similar (i.e. test of no interaction between group and time). The underlying assumptions behind a linear mixed model were checked by inspection of plots of random intercepts and residuals. For all outcomes except the EQ-5D 5L and the Major Depression Inventory, the assumptions were fulfilled, and hence we used the non-parametric bootstrap method with 1000 repetitions to compute p-values and 95% confidence interval's (CI) for these two measures. Three secondary analyses were conducted to examine the robustness of the primary

analysis: 1) adding waiting time to intervention start as a covariate (as waiting time differed between the two rehabilitation programmes by chance (10)), 2) replacing missing values by the average of non-missing scores at the particular time point, and 3) replacing missing values by the worst possible score (=100) in the integrated programme and the best possible score (=0) in the existing programme. Additionally, graphs including means at all nine measurement time points (t0-t8) were presented in order to illustrate changes over time for patients allocated to each rehabilitation programme.

Statistical significance was defined as $p \leq 0.05$. A statistical analysis plan was developed and finalised prior to data analysis (Supplementary file 1), and STATA 16 was used for all statistical analyses.

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 at ClinicalTrials.gov (identifier NCT02884466).

Results

The first rehabilitation programmes commenced in September 2016 and patients in the last rehabilitation programme reached their 1-year follow up in November 2019. In total, 165 patients were randomly allocated to the integrated programme (n=82) or to the existing programme (n=83) (Figure 2). There were no systematic differences in either baseline or outcome variables between patients lost to follow up and those who completed the 1-year follow up (data not shown).

[Insert Figure 2]

Baseline data and clinical characteristics were comparable between programmes (Table 2). For further details on baseline characteristics, see (10). There were no adverse events or deaths related to either of the rehabilitation programmes.

[Insert Table 2]

The mean difference of -0.53 (95% CI; -4.08; 3.02) in the change in back-specific disability between rehabilitation programmes was neither statistically nor clinically significant (Table 3).

[Insert Table 3]

No evidence of a difference in development in ODI score over time was found ($\chi^2(3) = 0.12$, p-value = 0.989) (Figure 3). Further, there were no statistically significant differences between

rehabilitation programmes for any of the secondary outcomes at the 1-year follow up (Table 3). Figures illustrating the secondary outcomes are provided in Supplementary file 2.

[Insert Figure 3]

In the integrated programme, the average decrease in Oswestry Disability Index scores was from 42 (95% CI: 39; 44) at baseline to 37 (95% CI: 34; 40) at the 1-year follow up. In the existing programme the average decrease in Oswestry Disability Index scores was from 43 (95% CI: 40; 45) at baseline to 39 (95% CI: 36; 41) at the 1-year follow up.

Neither the secondary analysis adjusted for waiting time, nor the secondary analyses replacing missing values by the average of non-missing scores at the particular time point changed the primary result. Replacing missing values by the worst possible score (=100) for the integrated programme and by the best possible score (=0) for the existing programme changed the results (mean difference: 19.79 (95% CI: 13.80; 25.77), p = 0.000).

The outcome trajectories including all measurement time points from t0-t8 illustrate that mean changes over time were similar in patients in both rehabilitation programmes (Figure 4).

[Insert Figure 4]

Discussion

At 1-year follow up, the integrated programme comprising inpatient stays alternating with home-based activities and booster sessions did not improve back-specific disability or any other outcomes in patients with chronic low back pain when compared with an existing four-week inpatient programme. The results are in line with those from the 6-month follow up (10). However, as they are contrary to our hypothesis, they warrant scrutiny, not only because of design choices for the integrated programme, but also of the evidence base upon which the integrated programme was built.

In terms of design choices, the integrated programme was designed to support the integration of knowledge, skills, and behaviours, acquired during an inpatient stay, into the daily life of the patient. The justification for the integrated programme was based on a thorough development process and feasibility testing following the Medical Research Council's guidance on complex interventions (20).

In the development stage, firstly, we drew on recent clinical guidelines (2, 3) and other evidence (4) confirming that multidisciplinary rehabilitation is recommended as a second-line

treatment for patients with chronic low back pain. Secondly, we identified the biopsychosocial approach (5, 7) and the Chronic Care Model (8) as recognised theories to justify the way in which the integrated programme was delivered. Finally, when modelling processes and outcomes, we aimed for a high degree of patient and public involvement. Scrutinising the development stage, in general, it still seems as a reasonable foundation upon which to build the integrated programme. However, the particular theories (5, 7, 8) underpinning the integrated programme, and the primary outcome measure chosen (16) could be questioned. In terms of the biopsychosocial approach (5, 7), a Cochrane review (4) found evidence favoring multidisciplinary rehabilitation when aligned with the biopsychosocial model. Furthermore, the biopsychosocial approach has been widely accepted as appropriate in patients with chronic low back pain since the 1980s (21), and it still is (6).

The potential for better outcomes was based on adding booster sessions underpinned by the Chronic Care Model (8). When it comes to adding booster sessions to interventions delivered to patients with musculoskeletal conditions, the evidence is equivocal, and thus, questionable (22-26). The choice of the Oswestry Disability Index as the primary outcome also warrants elaboration. The lack of any difference may be explained by the fact that since the integrated programme aimed at integrating knowledge, skills and behaviours into the patients' daily lives, it may have been better for the primary outcome to measure these domains. There was, however, no validated outcome measures to capture this. Furthermore, we wished to evaluate an outcome which is broadly acknowledged in this population. Thus, achieving improvements in disability and other outcomes, were seen as proxies of successful integration of knowledge, skills and behaviours. Given the broad biopsychosocial coverage of the different outcomes used in the trial, and the consistent finding of no between-group differences, it is therefore unlikely that the result of the trial would have been different had we selected a different primary outcome.

The feasibility stage resulted in fine-tuning of the administrative procedures, and following that, we believed that the integrated programme had the potential to be successfully implemented and evaluated. However, an integrated process evaluation revealed unexpected challenges and, with the value of hindsight, running a pilot randomised controlled trial would have been beneficial. The process evaluation revealed challenges implementing important elements of the integrated programme (pamphlet and phone calls) which were developed to support the intended integration of knowledge, skills, and behaviours into the patient's daily life. Further, it revealed administrative challenges, including postponements and non-adherence at the 6-month follow up. With these findings, it became obvious that the logistics of implementing the integrated programme

in daily clinical practice was a challenge. This could potentially have caused bias in favour of the existing programme.

In terms of the evidence base, six trials comparing two or more rehabilitation programmes in patients with chronic low back pain using disability as the primary outcome were identified (22, 27-31). These trials had some substantial differences. Firstly, the populations included had different levels of disability at baseline. Secondly, four different measurements (the Oswestry Disability Index (27, 28), the Roland Morris Disability Questionnaire (30, 31), the Quebec Back Pain Disability Scale (29), and the Pain Disability Index (22)) were used. Thirdly, some compared different dose and content (28-30), and some compared identical rehabilitation programmes but added a further component to one of the rehabilitation programmes e.g. involvement of spouses (31), more specifically tailored interventions (27), or subsequent booster sessions (22). Lastly, two trials had short-term follow up (3 months or less) (27, 28), others medium-term follow up (3 to less than 12 months) (29, 30), and yet others incorporated long-term follow up (12 months or more) (22, 27, 30, 31). These differences limit direct comparison with the current trial. However, regardless of the differences, the results of the six trials were similar to the current trial, namely no significant differences in disability when comparing two or more rehabilitation programmes.

In general, evidence indicates that rehabilitation as a process is beneficial (32), and it supports the effect of rehabilitation in the field of chronic low back pain (1-4). However, when adding our results to the current evidence base, it seems difficult to demonstrate if and how much dose, content and delivery of a specific multidisciplinary rehabilitation programmes matters (32). It could be discussed whether the reasons for the repeated null effect in the trials could be due to trial features or quality. Rather, it should be considered whether it is owing to the comprehensive nature of the rehabilitation programmes being compared, or whether the complex interplay between person-specific biopsychosocial factors driving disability in patients with chronic low back pain makes it difficult to improve disability with programmes that more or less are one-size-fits-all (32).

The trial had several strengths including randomisation and allocation concealment, the two-arm parallel design, blinding of the researcher performing the statistical analysis, high adherence and follow-up rates, as well as equal lost to follow-up rates in the two rehabilitation programmes. Further strengths are the thorough development and feasibility tests of the integrated programme including patient and public involvement and a process evaluation (10), the use of the TIDieR checklist to justify and describe the integrated programme (9), and the preparation of a

statistical analysis plan (Supplementary file 1).

One limitation of the trial is the lack of measured adherence to home-based activities. Hence, whether patients from the integrated programme actually did integrate acquired knowledge, skills and behaviours into their daily lives was not directly evaluated. Another limitation was the risk of contamination, since the trial was delivered by non-blinded providers to non-blinded patients in the same rehabilitation centre, at the same time, and whether providers and patients in the existing programme were inspired by the integrated programme and patients took the opportunity to integrate knowledge, skills and behaviours into their daily lives is unknown.

Providers and decision-makers ought to know, and patients need to be reassured, that evidence supports the effectiveness of multidisciplinary rehabilitation (1-4, 32). Currently, there is no evidence to guide the decision about the most optimal way to deliver a multidisciplinary rehabilitation programme for patients with chronic low back pain. In light of the plethora of research in this field, new intervention studies are probably not the best solution address this challenge. Maybe we need to gain a wider perspective and look into new actions required by the political, public health, and health care systems (33).

Clinical messages

- Changing the delivery of an inpatient rehabilitation programme does not lead to improved long-term back-specific disability for patients with chronic low back pain.
- Chronic low back pain is driven by biopsychosocial factors, and it seems challenging to target each individual patient primarily with a one-size-fits-all approach.

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Table 1. Differences and similarities between the integrated programme and the existing programme.

Differences		
Characteristics	Description	
	Integrated programme	Existing programme
Delivery of the rehabilitation programme	1) pre-admission day 2) two weeks of home-based activities 3) two-week inpatient stay 4) four weeks of home-based activities 5) initial two-day inpatient booster session 6) six weeks of home-based activities 7) second two-day inpatient booster session 8) 6-month follow-up visit In total 15 inpatient days. In between the inpatient stays, patients were at home (in total, 11 weeks). The integrated programme lasted for 14 weeks. During the integrated programme, continuous focus was on integration of knowledge, skills and behaviours into daily life supported by the home-based activities.	1) 4-week inpatient stay 2) 6-month follow-up visit In total, 21 inpatient days. The existing programme lasted for 4 weeks. At the end of the existing programme focus was on the integration of knowledge, skills and behaviours into daily life.
Elements to support integration of knowledge, skills and behaviours	- Pamphlet - A phone call half-way through each home-based period (in total, two phone calls)	-

	- Focus on integration during the inpatient stays, but especially in the clinical activities comprising individual counselling.	
Development of the rehabilitation programme	A systematic research process following the MRC's guidance on developing and evaluating complex interventions.	Not developed using a systematic research process.
Patient and public involvement	A major part of the development, feasibility-test and evaluation.	-
Theoretical underpinning	The biopsychosocial approach and the Chronic Care Model.	The biopsychosocial approach.
Similarities		
Characteristics	Description	
Rehabilitation programmes for patients with a variety of rheumatic health conditions	The rehabilitation programmes encompassed the four actions characterising the process of rehabilitation: 1) assessment, 2) goal setting, 3) intervention, and 4) evaluation (Section 1.4).	
Clinical activities	38 clinical activities targeted the biopsychosocial factors driving disability. Some of the clinical activities were delivered more than once.	
Providers	The multidisciplinary team consisted of six physiotherapists, three occupational therapists, three nurses (educated as coaches and primarily focusing on the psychologic aspect of the programme), a rheumatologist, and a nutritional counsellor. The majority of the providers were trained in Motivational Interviewing.	
Contact hours	Identical in the two rehabilitation programmes (approximately 50 contact hours).	
Mode	A combination of group lecture and dialogue, group sessions (supervised and non-supervised), individual counselling and unsupervised individual exercise.	

Setting	A rehabilitation centre in Denmark.
Tailoring	The rehabilitation programmes were partially standardised and partially tailored, the latter to ensure a degree of person-centeredness. The tailoring occurred primarily during: 1) the clinical assessment (including goal setting), 2) the multidisciplinary conference, 3) individual counselling, and 4) exercise and physical activity sessions.
Additional contact	Permission to contact the providers twice via the exercise app.

Table 2. Characteristics of the sample at baseline.

	Integrated programme n=82	**Existing programme n=83**
Sex (women) n (%)	60 (72)	60 (73)
Age (years) Mean (SD) [Range]	49 (13) [22-72]	51 (13) [25-84]
Leg pain n (%)	65 (79)	59 (71)
Disability* ODI (0-100) Mean (SD) [Range]	42 (10) [20-68]	43 (11) [24-72]
Back pain intensity NRS (0-10)** Mean (SD)	6 (2)	6 (2)
Pain Self-efficacy PSEQ (0-60) Mean (SD)	28 (11)	27 (10)
Quality of life EQ-5D 5L (-0.624-1) Mean (SD)	20 (11)	20 (11)
Depression MDI (0-50) Mean (SD)	20 (12)	20 (11)

*Due to technical issues in the database, one patient with an ODI score of 20 was included.
**Mean back pain intensity for the last two weeks.
ODI: Oswestry Disability Index
NRS: Numerical Rating Scale
PSEQ: Pain Self-Efficacy Questionnaire
EQ-5D 5L: EuroQol-5 Domain 5-level
MDI: Major Depression Inventory

Table 3.

Summary of 1-year follow-up data on between-group and within-group differences on primary and secondary outcomes.

	Between-group		Within-group	
	Mean difference* (95% CI)	p-value	Integrated programme Mean (95% CI)	Existing programme Mean (95% CI)
Primary outcome				
Disability (ODI)	-0.53 (-4.08 to 3.02)	0.770	-4.55 (-7.08 to -2.02)	-4.02 (-6.51 to -1.53)
Secondary outcomes				
Pain intensity** (NRS)	-0.10 (-0.68 to 0.48)	0.727	-0.58 (-1.00 to -0.17)	-0.48 (-0.89 to -0.07)
Pain Self-Efficacy (PSEQ)	0.01 (-3.34 to 3.37)	0.994	4.43 (2.05 to 6.82)	4.42 (2.07 to 6.78)
Health-related quality of life (EQ-5D 5L)***	0.02 (-0.04 to 0.07)	0.558	0.04 (0.00 to 0.07)	0.02 (-0.01 to 0.06)
Depression (MDI)***	1.67 (-1.52 to 4.85)	0.305	-1.79 (-3.96 to 0.38)	-3.45 (-5.80 to -1.11)

*Mean difference (integrated programme – existing programme) estimated from linear mixed models
**Mean pain intensity for the last two weeks
***When analysing EQ-5D 5L and MDI non-parametric bootstrap method with 1000 repetitions to compute p-values and 95% CI's was used.
ODI: Oswestry Disability Index
NRS: Numerical Rating Scale
PSEQ: Pain Self-Efficacy Questionnaire
EQ-5D 5L: EuroQol-5 Domain 5-level
MDI: Major Depression Inventory

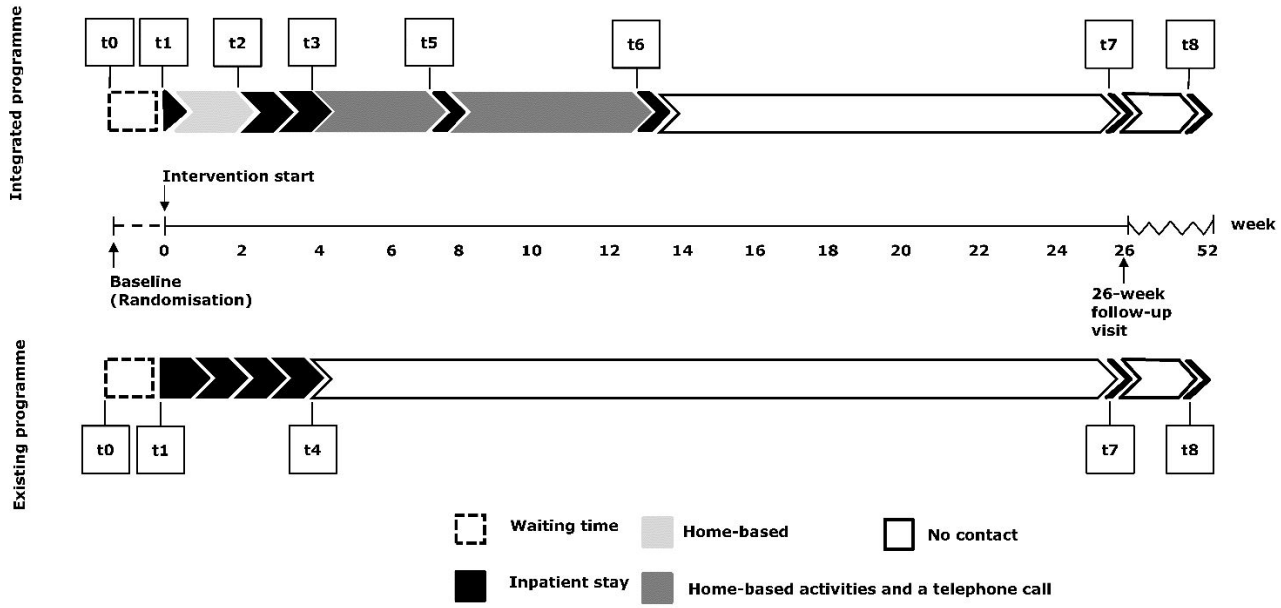
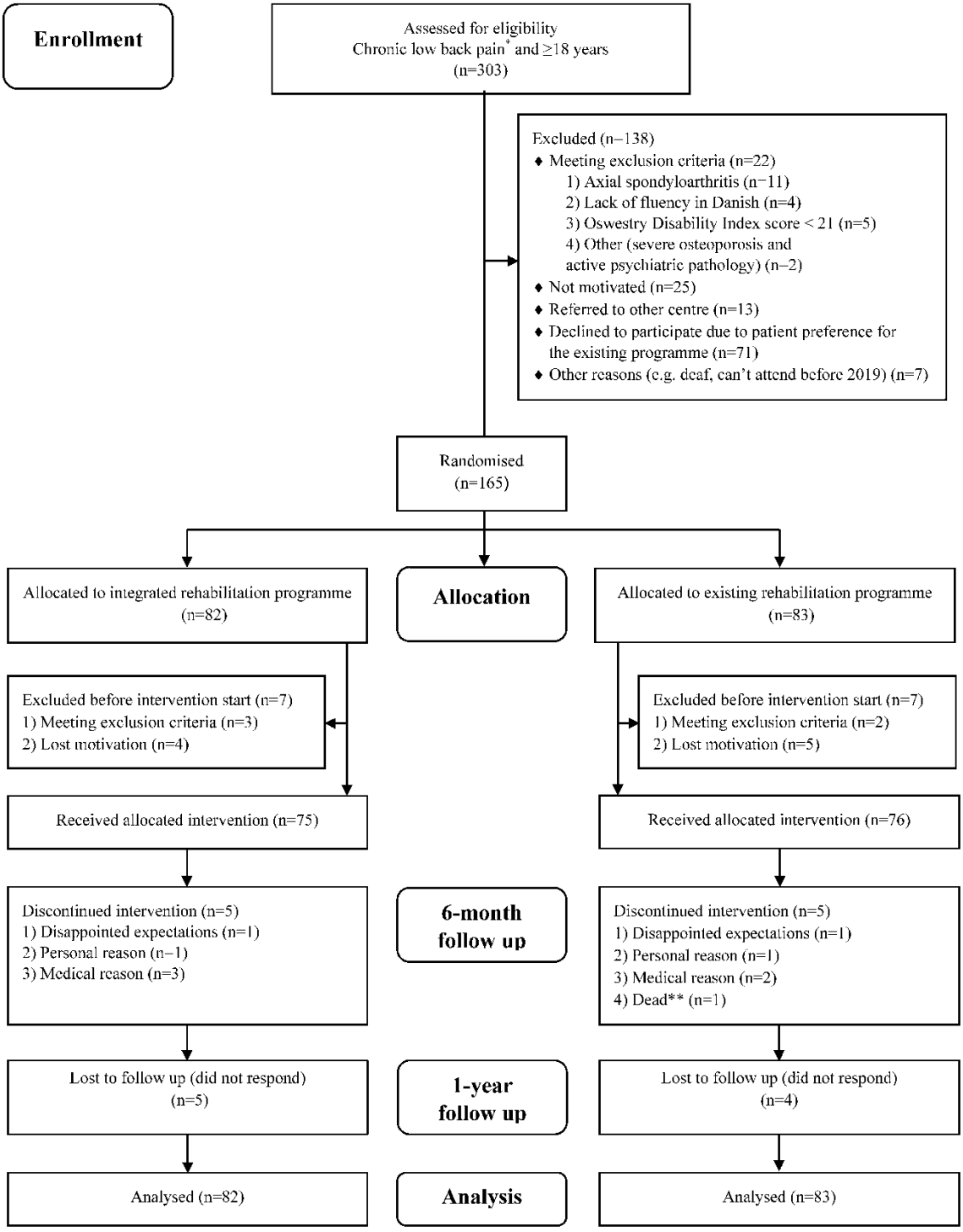


Figure 1. The integrated programme and the existing programme with related measurement time points.



* The following ICD-10 diagnosis codes for diseases, signs and symptoms related to chronic low back pain were used: DM40, DM41, DM42, DM43 (not 43.3, 43.4, 43.6), DM47, DM48, DM51, DM53 (not 53.0, 53.1), DM54 (not 54.0, 54.2, 54.6), DM96.1 and DT91.0.
** The reason for dead was unrelated to the trial.

Figure 2. Flow-chart of participants through the trial.

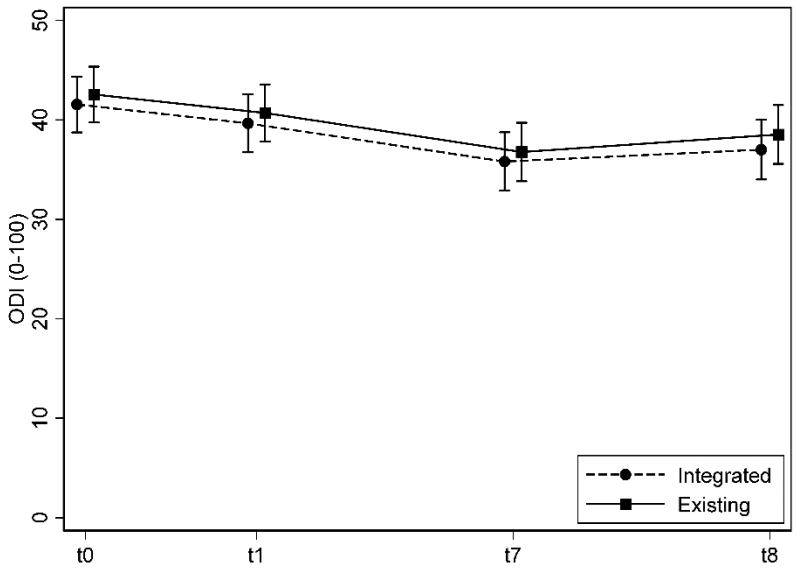


Figure 3. Mean back-specific disability measured by the Oswestry Disability Index (ODI) during the 1-year follow-up period including the four identical measurement time points: t0 = baseline, t1 = before intervention start, t7 = before the 6-month follow-up visit, and t8 = at the 12-month follow up (from the linear mixed model). The time between t0-t1 was 16 weeks (=mean waiting time), the time between t1-t7 and between t7-t8 was 6 months.

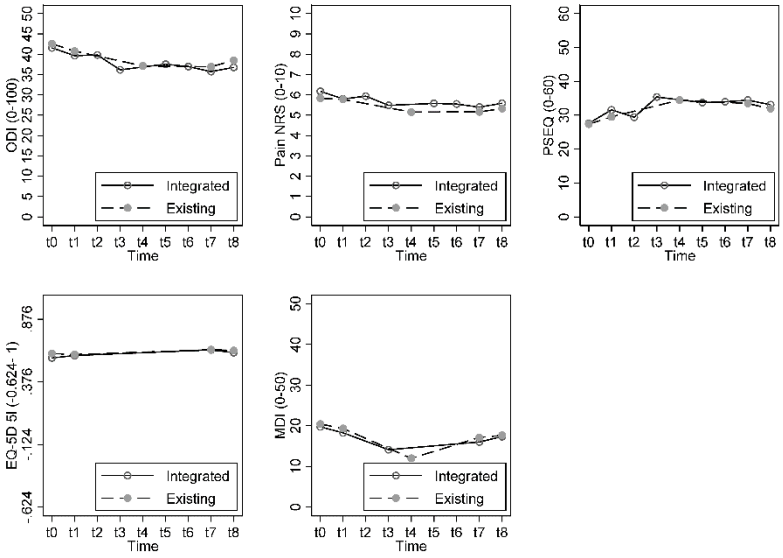


Figure 4. Mean changes over the 1-year follow-up period, including all nine measurement time points (t0-t8). Notice that the time between the measurement time points are displayed as equidistant even though they were not. t0 = baseline, t1 = before the pre-assessment day (integrated programme) and before the 4-week inpatient stay (existing programme), t3 = the end of the 2-week inpatient stay (integrated programme), t4 = the end of the 4-week inpatient stay (existing programme), t5 = before the initial booster session (integrated programme, t6 = before the second booster session (integrated programme), t7 = before the 6-month follow-up visit (integrated programme + existing programme), and t8 = at the 12-month follow up (integrated programme + existing programme).

ODI: Oswestry Disability Index

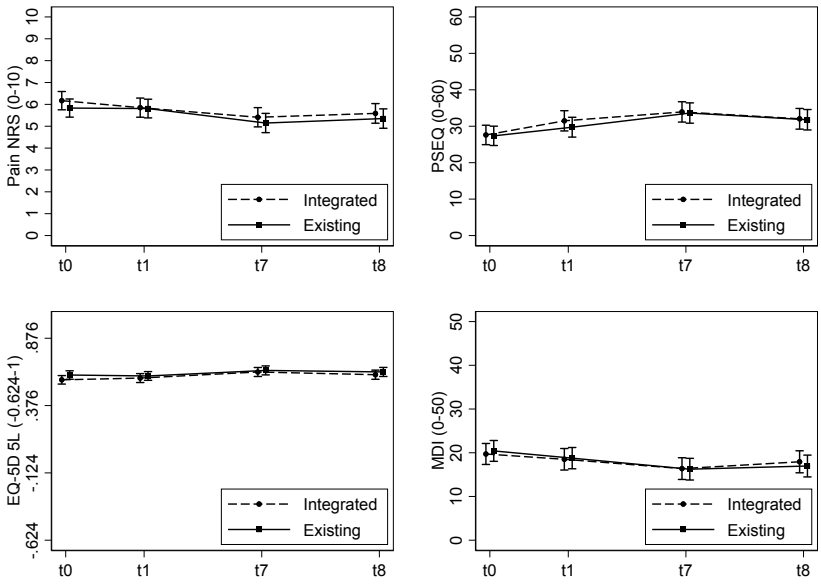
NRS: Numerical Rating Scale

PSEQ: Pain Self-Efficacy Questionnaire

EQ-5D 5L: EuroQol-5 Domain 5-level

MDI: Major Depression Inventory

Supplementary file 2



Mean changes in secondary outcomes during the 12-month follow-up period including the four identical measurement time points: t0 = baseline, t1 = before intervention start, t7 = before the 6-month follow-up visit (6 months after the start of the rehabilitation programme), and t8 = 12 months after the start of the rehabilitation programme. The time between t0-t1 was 4 months (= mean waiting time), the time between t1-t7 and between t7-t8 was 6 months.

NRS: Numerical Rating Scale

PSEQ: Pain Self-Efficacy Questionnaire

EQ-5D 5L: EuroQol-5 Domain 5-level

MDI: Major Depression Inventory

Appendix 4

fr 15-05-2020 12:50
Peter Craig <Peter.Craig@glasgow.ac.uk>
Re: Permission to use Figure 1 from MRC guidance on complex interventions in dissertation

Dear Anne Marie
You are welcome to use fig 1. Please include the following acknowledgement: Reproduced with permission of the UK Medical Research Council.
Good luck with completing your dissertation.
Kind regards
Peter

Peter Craig
Senior Research Fellow
Informing Healthy Public Policy

MRC/CSO Social and Public Health Sciences Unit
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Improving health and reducing inequalities through the study of social influences on health and wellbeing.

University of Glasgow CHIEF SCIENTIST OFFICE MRC Medical Research Council

---

From: Anne Mette Schmidt <aschmidt@sanocenter.dk>
Sent: 15 May 2020 11:26
To: Peter Craig <Peter.Craig@glasgow.ac.uk>
Subject: Permission to use Figure 1 from MRC guidance on complex interventions in dissertation

Dear Peter Craig
I have learned that you are the lead author of the MRC guidance on the development and evaluation of complex interventions. I am a Danish PhD candidate who have found great inspiration in the guidance. In relation to that, I want to ask for your permission to use Figure 1 (Key elements of the development and evaluation process) from the guidance in my dissertation.
I am looking forward to your answer.
Regards Anne Mette

Anne Mette Schmidt
Ph.D studerende | Sano Århus

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Appendix 5

Patient and public involvement (PPI) in the development, feasibility-testing and evaluation of the trial reported following "Guidance for Reporting Involvement of Patients and the Public"[1].

Section and topic	Item
1: Aim Report the aim of PPI in the study	To consult and collaborate with patients, providers, administrative and management staff (together termed "stakeholders") as research partners in the development, feasibility-testing and evaluation of the current trial.
2: Methods Provide a clear description of the methods used for PPI in the study	Patients were included consecutively where it made sense and were practically possible. The patients involved had lived experience with CLBP; most of them had concrete experiences with the existing programme, whereas others had concrete experience with the integrated programme. All providers, administrative and management staff employed during the trial period were consecutively involved, sometimes together and sometimes in specialised groups. Several face-to-face meetings were held and data were collected and stored in meeting summaries and the field notes of the researcher responsible. In order to calculate sample size, 12 patients attending the existing programme completed the Oswestry Disability Index at the beginning and at the end of the programme.
3: Study results Outcomes—Report the results of PPI in the study, including both positive and negative outcomes	PPI contributed to the trial in several ways: Development stage - All stakeholders gave input to and "approved" the structure of the integrated programme. - Patients and providers suggested primary and secondary outcomes which in combination with international recommendations lead to the researchers final decision about outcome measurements. - Providers preferred Pain Self-Efficacy Queastionnaire above other outcome measures when measuring the psychological outcome. - Patients read and commented on the participant information and informed consent form leading to some refinements. Feasibility-testing stage - Patient's were involved in feasibility testing the database set-up and their comments about e.g. abbreviations and functionalities were integrated on a large scale in the final database set-up. - Patients, administrative and management staff were involved in fine-tuning administrative procedures including revision of the welcome letter, e-mail wording, how to document informed consent in the electronic health record, description of the inclusion work procedure and work procedure for booking the inpatient stays. Furthermore, a person responsible for the phone calls before each booster sessions was nominated as well as a person responsible for handing out electronic tablets in order to facilitate data collection. - Patients requested access to non-supervised aqua gymnastic to a frequency identical to that of the existing programme, a place to rest on

	the pre-assessment day and the day of the 26-week follow up, and a specific place to sit in the dining room. The requests were fulfilled. - The administrative and management staff were involved in the decision to overbook each integrated programme with 2-3 patients due to postponement of approximately 20% of all scheduled appointments in the existing programme. - Based on feedback from all stakeholders, the population of interest and their intended willingness to participate was deemed large enough to recruit a sufficient number of eligible patients. - Sample size was estimated based on mean ODI change score and SD from 12 patients attending the existing programme. Evaluation stage - All stakeholders were asked for feedback on the integrated programme throughout the evaluation, resulting in minor adjustments e.g. the sender of the e-mail containing the questionnaires was changed.
4: Discussion and conclusions Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	We believe that PPI influenced the trial in several positive ways. All stakeholders were continuously involved in the development and feasibility-testing of the trial resulting in a large degree of influence. This is considered to have had an impact on important aspects of the trial including the low number of patients not completing and considerable support from providers, administrative and management staff when trial begun. The consecutive inclusion of patients is seen as a strength, as it reflects the diversity of patients attending the rehabilitation centre. We decided not to provide PPI training for the patients, as we wanted the patients to contribute with their lived experiences as patients, and not as "professional patients". No reimbursement was offered to patients; all patients asked to participate in PPI were pleased to be involved and participated as they felt they could help other patients. The management staff made it possible to prioritise involvement of providers and administrative staff despite no additional resources.
5: Reflections/critical perspective Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	PPI was embedded as far as was possible in the development, feasibility testing and evaluation of the trial, which is considered a strength as it is expected to minimise the risk of research waste and to increase the value of the research. Neither the stakeholders nor the project team involved in this trial had any prior experiences with PPI in research, but everybody was interested in and curious about PPI and dedicated to, and engaged with, the task. PPI gave us new ideas, it deepened our understanding of what mattered to the patients, providers, administrative and management staff and it helped us to identify and hopefully avoid problems we may not have anticipated.

1. Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *BMJ (Clinical research ed)* 2017; 358: j3453. 2017/08/05. DOI: 10.1136/bmj.j3453.

Appendix 6

Statistical Analysis Plan

Section 1: Administrative Information

Title and trial registration

1a Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and trial acronym (if applicable)

Tentative title:

The Sano study: Evaluation of an integrated rehabilitation programme including booster sessions in patients with chronic low back pain - a randomized controlled trial

1b Trial registration number

The study has been registered at Clinical Trials.gov (identifier NCT02884466).
https://register.clinicaltrials.gov/prs/app/template/EditProtocol.vm?listmode=Edit&uid=U00038YJ&ts=3&sid=S0006HC8&cx=-1lel7y

Notice:

Statistical analysis plan, and how adherence is to be assessed doesn't appear from the ClinicalTrials registration.

SAP version

2 SAP version number with dates

Version 3 – 20.02.19

Version 3 – 10.04.19 (Danish comments removed)

Version 4 – 13.05.19

Protocol version

3 Reference to version of protocol being used

See the latest protocol version.

SAP revisions

4a SAP revision history

SAP_Draft (October-December 2018)

SAP_version1_17.01.19

SAP_version2_06.02.19

SAP_version3_20.02.19

SAP_version4_13.05.19

4b Justification for each SAP revision

The SAP_Draft (October-December 2018) was revised prior to statistical supervision. This lead to:
SAP_version1_17.01.19
Corrections following statistical supervision (04.02.19) lead to (analyses method):
SAP_version2_06.02.19
Corrections following supervision (20.02.19) lead to (categorization of variables in table 1 and decision about analyses time/period):
SAP_version3_20.02.19
Corrections following supervision (13.05.19) lead to (decisions about ITT><mITT + secondary analyses):
SAP_version4_13.05.19

4c Timing of SAP revisions in relation to interim analyses, etc

Roles and responsibility

5 Names, affiliations, and roles of SAP contributors

The SAP is composed by Anne Mette Schmidt with contributions from Thomas Maribo (main supervisor) and Niels Trolle (statistician).

Signatures of

6a Person writing the SAP
6b Senior statistician responsible
6c Chief investigator/clinical lead

Section 2: Introduction

Background and rationale

7 Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial

See the latest protocol version.

Objectives

8 Description of specific objectives or hypotheses

See the latest protocol version.

Section 3: Study Methods

Trial design

9 Brief description of trial design including type of trial (eg, parallel group, multiarm, crossover, factorial) and allocation ratio and may include brief description of interventions

See the latest protocol version.

Randomization

10 Randomization details, eg, whether any minimization or stratification occurred (including stratifying factors used or the location of that information if it is not held within the SAP)
See the latest protocol version.

Sample size

11 Full sample size calculation or reference to sample size calculation in protocol (instead of replication in SAP)
Oswestry Disability Index was used for sample size calculation. Based on data from the literature and a pilot study on 25 patients with CLBP from Sano, mean change was estimated to 10 in the intervention group and 5 in the control group, and the standard deviation on the changes was estimated to 10. Using 80% power and a significance level of 0.05, 64 participants was required in each group. A dropout rate of 20% was estimated, for what reason it was planned to recruit a total of 160 participants.

The number of included patients was extended in August 2018 to 165 to fill up both programmes during 2018. The extension was approved by The Central Denmark Region Committees on Biomedical and Research Ethics.

Framework

12 Superiority, equivalence, or non-inferiority hypothesis testing framework, including which comparisons will be presented on this basis
A superiority trail aiming to compare change in disability after 26 weeks in two groups of patients with chronic low back pain, comparing an existing rehabilitation programme to an integrated rehabilitation programme. Furthermore, to compare changes in the two rehabilitation programmes on pain, pain self-efficacy, quality of life, depression and exercise capacity.
The hypotheses is, that the integrated rehabilitation programme will experience a five points larger improvement in Oswestry Disability Index compared to existing rehabilitation programme. Furthermore, the integrated rehabilitation programme will experience a larger improvement in pain, pain self-efficacy, quality of life, depression and exercise capacity compared to existing rehabilitation programme.

Statistical interim analyses and stopping guidance

13a Information on interim analyses specifying what interim analyses will be carried out and listing of time points
13b Any planned adjustment of the significance level due to interim analysis
13c Details of guidelines for stopping the trial early
An interim analyses will not be done, as none of the programmes are suspected to cause any harm. Furthermore, the timeframe of the study does not allow for interim analyses.

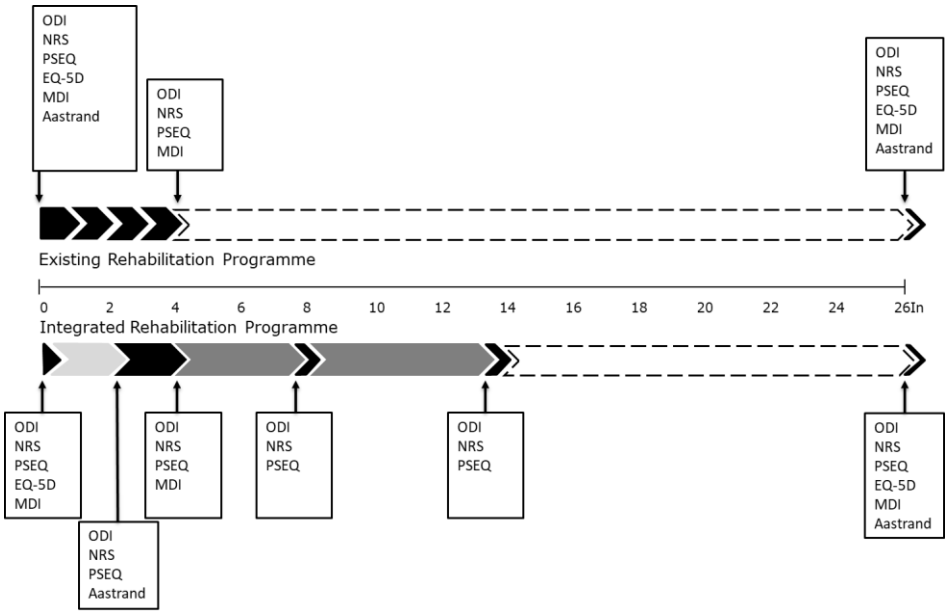
Timing of final analysis

14 Timing of final analysis, eg, all outcomes analyzed collectively or timing stratified by planned length of follow-up

Outcomes will be analyzed when all participants have completed 26-week follow-up by May 2019.

Timing of outcome assessments

15 Time points at which the outcomes are measured including visit "windows"



In addition to the measurement time points shown above, all PROM outcomes were measured before randomization (up to 10-12 months prior to intervention start due to waiting list). This time point is called "randomisation" (not shown in the figure above) and will be identical to baseline. At "randomisation" demographic variables were measured.

Furthermore, all PROM outcomes will be measured after 52 weeks – this measurement time point will not be a part of study 2 due to the timeframe.

Section 4: Statistical Principles

Confidence intervals and *P* values

16 Level of statistical significance

P values ≤ 0.05 will be considered statistically significant.

17 Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled

Adjustment for multiplicity will not be done as we have chosen one primary outcome, and as we are only comparing two programmes.

18 Confidence intervals to be reported

95% CI will be used consistently across outcomes.

Adherence and protocol deviations

19a Definition of adherence to the intervention and how this is assessed including extent of exposure

In pragmatic trials there is a larger degree of flexibility due to adherence. Therefore, our primary analysis will be conducted as a modified intention-to-treat analysis regardless of adherence to the inpatient stay. A per-protocol will be performed excluding non-adherent patients. The cut-off for adherence was set based on a pragmatic reasoning concluding that non-adherence for one booster session and one additional day (in all 3 inpatient days) was acceptable for patients attending the integrated programme. The integrated programme consists of 15 inpatient days and non-adherence of three days is identical to 20% of non-adherence, thus the cut-off for adherence was set at ≥ 80%. For patients allocated to the existing programme the same 80% cut-off was used. Thus, patients allocated to the integrated programme with adherence of ≥12 inpatient days and patients allocated to the existing programme with adherence of ≥ 17 inpatient days will be included as adherent patients in the per-protocol analysis.

Adherence to homebased activities in the integrated programme is not measured.

We are aware that attendance is not necessarily identical to adherence. Even though you are registered as being inpatient you can skip a few or more clinical activities as well as you can attend a clinical activity but not being "present" or adherent. Thus, adherence to each clinical activity is impossible to assess, but the outcomes chosen will hopefully serve as proxies for adherence.

19b Description of how adherence to the intervention will be presented

Adherence to the intervention will be presented as number and percentages of patients attending ≥80% of the inpatient days.

19c Definition of protocol deviations for the trial

Protocol deviation is attending < 80% of the inpatient days.

19d Description of which protocol deviations will be summarized

Patients attending <80% of the inpatient days will be presented as number and percentages of patients.

Analysis populations

20 Definition of analysis populations, eg, intention to treat, per protocol, complete case, safety

Modified intention to treat analysis will be performed (by original assigned groups) on all available data (complete case analysis) regardless of the degree of adherence.

Section 5: Trial Population

Screening data

21 Reporting of screening data (if collected) to describe representativeness of trial sample

The period recruiting, the total number of patients assessed for eligibility, the number of patients recruited, the number of screened patients not recruited, and the reason for non-recruitment will be reported in the text and/or in the CONSORT flow diagram.

Eligibility

22 Summary of eligibility criteria

See the latest protocol version.

Recruitment

23 Information to be included in the CONSORT flow diagram

The CONSORT flow diagram will be used.

Withdrawal/follow-up

24a Level of withdrawal, eg, from intervention and/or from follow-up

The level of consent withdrawal will be presented in the CONSORT flow diagram. Patients withdrew in a complete manner meaning that – no further follow-up or data collection were done.

24b Timing of withdrawal/lost to follow-up data

Will be presented in CONSORT flow diagram with numbers and reasons for withdrawal and/or exclusion given at each stage (before the intervention, during the intervention or 26-week follow-up).

24c Reasons and details of how withdrawal/lost to follow-up data will be presented

Will be presented in CONSORT flow diagram with numbers and reasons for withdrawal and/or exclusion given at each stage (before the intervention, during the intervention or 26-week follow-up).

Baseline patient characteristics (Table 1)

25a List of baseline characteristics to be summarized

Demographics	**Answers**	
Gender (women)	N%	
Age	Mean (SD) (and range)	
Have you attended Sano or another identical rehabilitation programme previously?	n(%) (*) (*=how many n(%) have attended Sano before)	
Marital status	1	Married
	2	Single + widow
Smokers	1	Yes
	2	No
Work status (Further categorization is needed)	1	I ordinær beskæftigelse
	2	Ledig
	3	I fleksjob eller i løntilskud mv.
	4	Kontanthjælpsmodtager/Dagpengemodtager
	5	Under uddannelse, SU, lærling, elev mv
	6	Sygedagpengemodtager
	7	I afklarings- eller ressourceforløb el.lign. om fremtidig forsørgelse
	8	Førtidspensionist
	9	Efterlønsmodtager, på overgangsydelse eller folkepensionist
	10	På orlov (barselsorlov, uddannelsesorlov m.v.)
	11	Hjemmearbejdende (uden andet arbejde)
	12	Ingen indtægt
Education	1	Low (Folkeskole/mellemskole + Studentereksamen/HF-eksamen)
	2	Middle (Faglært indenfor håndværk, handel, kontor (fx lærlinge- eller Efg-uddannelse) + Kort videregående uddannelse under 3 år (fx social- og sundhedsassistent, teknikker) + Mellemlang videregående uddannelse 3-4 år (fx skolelærer, journalist, socialrådgiver))
	3	High (Lang videregående uddannelse på 5 år eller mere (fx cand. mag., læge, psykolog))
	4	Don't know
Do you have an ongoing compensation claim due to your health status/problem?	1	Yes
	2	No
Disability (ODI)	Sumscore (0-100)	

(Mean (SD))	
Back pain (0-10) (NRS) (Mean (SD))	Level of low back pain right now/at the moment Level of worst low back pain during the last two weeks Level of average low back pain during the last two weeks
Pain radiation to the legs during the last two weeks (n(%))	1. Yes 2. No 3. I dont know
Quality of life (EQ-5D) (Mean (SD))	Sumscore
Pain Self-efficacy (PSEQ) (Mean (SD))	Sumscore (0-60)
Depression (MDI) (Mean (SD))	Sumscore (0-50)
Daily activity level	Three questions about daily activity level with seven possible answer categories.
Variables that will not be presented (even though measured)	Which rehabilitation programme was previously attended, alcohol and support from relatives. Additionally satisfaction with allocation (measured at intervention start and can therefore be influenced by waiting time.

25b Details of how baseline characteristics will be descriptively summarized
The included study population will be described in a table 1 without p-values (according to test for baseline differences see Michiel de Boer ”Testing for baseline differences” International journal of behavioural nutrition and physical activity, 2015). Tabel 1 will be divided into six collumns presenting patients randomized according to allocated group, patients completing the study (independent of attendance/adherence) according to allocated group and patients randomized/included but not completing the study (=drop-outs).
Differences in demographic and PROM will be compared between patients completing the study and drop-outs.
Differences in personal (sex and age) and disease characteristic (diagnosis) will be compared between patients randomized and patients refused to participate in the study.
Baseline characteristics will be descriptively summarized and presented by mean (SD), median (IQR) or number (%).

Section 6: Analysis

Outcome definitions
List and describe each primary and secondary outcome including details of:

26a specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (eg, order in which they will be tested).
Primary outcome:

- Disability

Secondary outcomes:

- Pain
- Pain self-efficacy
- Quality of life
- Depression
- Daily activity level
- Exercise capacity

Furthermore, the following variables will be collected:

- Demographics (see Table 1)
- Clinical and neurological findings collected by an experienced rheumatologist using a standardized examination protocol, will be collected at the first inpatient contact. Data not used in the present study.

26b specific measurement and units (eg, glucose control, hbA1c [mmol/mol or %])

Primary outcome:

- Disability assessed by the Oswestry Disability Index, a 10-item scale where high score reflects great disability.

Secondary outcomes:

- Pain assessed quantitatively with Numerical Rating Scale.
- Pain self-efficacy measured by The Pain Self-Efficacy Questionnaire.
- Quality of life measured by EQ-5D.
- Depression measured by Major Depression Inventory.
- Daily activity level measured by three questions (https://www.fysio.dk/nyheder/2014/Hvordan-sporger-du-ind-til-patienternes-aktivitetsniveau)
- Exercise capacity measured by Aastrands cycle test.

All outcomes are continuous.

26c any calculation or transformation used to derive the outcome (eg, change from baseline, QoL score, time to event, logarithm, etc)
Outcomes will be measured as changes from baseline (=randomisation) to 26-week follow-up.

Analysis methods
27a what analysis method will be used and how the treatment effects will be presented
Regression analyses will be used as this gives a more precise estimate than t-test.
Primary analyses (between-group change): from randomisation to 26-week adjusted for the corresponding baseline value of the present outcome.

Furthermore, within-group changes will be described with mean change and SD for each group (simple linear regression).

Estimates and related 95% CI's and p-values will be reported.

27b any adjustment for covariates
- See 27a (will be done in the primary analysis)
- Exploratory analysis: adding waiting time as a covariate to the primary regression analysis

27c methods used for assumptions to be checked for statistical methods
Assumptions of the applied statistical tests will be assessed/checked as this is necessary for the test to be valid and the conclusions drawn from the analysis to be correct.

27d details of alternative methods to be used if distributional assumptions do not hold, eg, normality, proportional hazards, etc

27e any planned sensitivity analyses for each outcome where applicable

A sensitivity analyses (ITT) will test the robustness of the primary complete-case analysis. All drop-outs were complete meaning that no further follow-up or data collection were done and as a consequence imputation (last value carried forward) will be done.

27f any planned subgroup analyses for each outcome including how subgroups are defined
See 19a according to the described per protocol analysis comparing everybody><patients completing 26-week follow up + with adherence of >=80%.
See: Petticrew, 2011 "Damned if you do, …." – pitfalls of subgroup analysis

Missing data
28 Reporting and assumptions/statistical methods to handle missing data (eg, multiple imputation)
See 27e.

Additional analyses
29 Details of any additional statistical analyses required, eg, complier-average causal effect analysis
Nothing in addition to the above mentioned.

Harms
30 Sufficient detail on summarizing safety data, eg, information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analyzed, ie, grade 3/4 only, incidence case analysis, intervention emergent analysis
Cases of death or adverse events (reported by the rheumatologist) will be reported. (As the clinical activities are identical, this is not thought to cause a difference between the two programmes.)

Statistical software
31 Details of statistical packages to be used to carry out analyses
For statistical analysis, STATA (version 15) will be used.

References
32a References to be provided for nonstandard statistical methods
32b Reference to Data Management Plan
32c Reference to the Trial Master File and Statistical Master File
32d Reference to other standard operating procedures or documents to be adhered to

Appendix 7

Statistical Analysis Plan (Paper 3)

Section 1: Administrative Information

Title and trial registration

1a Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and trial acronym (if applicable).

Tentative title:

12 months follow-up from a randomised controlled trial comparing an integrated multidisciplinary rehabilitation programme alternating inpatient interventions with home-based activities to/with an existing 4-week inpatient programme for patients with chronic low back pain.

1b Trial registration number

The study has been registered at Clinical Trials.gov (identifier NCT02884466).
https://register.clinicaltrials.gov/prs/app/template/EditProtocol.vm?listmode=Edit&uid=U00038YJ&ts=3&sid=S0006HC8&cx=-1lel7y

Notice:

Statistical analysis plan, and how adherence is to be assessed doesn't appear from the ClinicalTrials registration.

SAP version

2 SAP version number with dates

Version 2 – 03.10.19

Version 1 – September 2019

Protocol version

3 Reference to version of protocol being used

See the latest protocol version.

SAP revisions

4a SAP revision history

Version 2 – Revised after statistical supervision 02.10.19

Version 1 – Draft

4b Justification for each SAP revision

Version 1 was formulated as a draft prior to statistical supervision.

Corrections following statistical supervision (02.10.19) lead to: Version 2

4c Timing of SAP revisions in relation to interim analyses, etc

Roles and responsibility

5 Names, affiliations, and roles of SAP contributors

The SAP is composed by Anne Mette Schmidt with contributions from Thomas Maribo (main supervisor) and Jens Søndergaard Jensen (statistician).

Signatures of

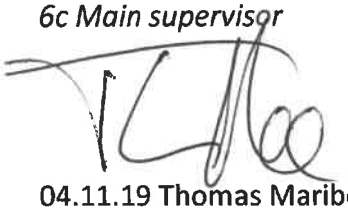
6a Person writing the SAP

04.11.19 Anne Mette Schmidt

6b Senior statistician responsible

04.11.19 Jens Søndergaard Jensen

6c Main supervisor



04.11.19 Thomas Maribo

Section 2: Introduction

Background and rationale

7 Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial

An integrated rehabilitation programme was developed and found feasible taking into account the existing evidence base, appropriate theories, and patient and public involvement. The integrated programme encompasses inpatient activities supported by a multidisciplinary team, and integration of knowledge, skills and behaviours in the patient's everyday life.

Objectives

8 Description of specific objectives or hypotheses

The aim of this paper 3 was to compare the effectiveness of an integrated rehabilitation programme with an existing rehabilitation programme in patients with chronic low back pain at 52-week follow-up.

Section 3: Study Methods

Trial design

9 Brief description of trial design including type of trial (eg, parallel group, multiarm, crossover, factorial) and allocation ratio and may include brief description of interventions

A single-centre, pragmatic, two-arm parallel randomised controlled trial.

Randomization

10 Randomization details, eg, whether any minimization or stratification occurred (including stratifying factors used or the location of that information if it is not held within the SAP)

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 41 in order to achieve approximate balance in mean disability levels in the arms of the trial.

Sample size

11 Full sample size calculation or reference to sample size calculation in protocol (instead of replication in SAP)

Oswestry Disability Index was used for sample size calculation. Based on data from the literature and a pilot study on 25 patients with CLBP from Sano, mean change was estimated to 10 in the intervention group and 5 in the control group, and the standard deviation on the changes was estimated to 10. Using 80% power and a significance level of 0.05, 64 participants was required in each group. A dropout rate of 20% was estimated, for what reason it was planned to recruit a total of 160 participants.

The number of included patients was extended in August 2018 to 165 to fill up both programmes during 2018. The extension was approved by The Central Denmark Region Committees on Biomedical and Research Ethics.

Framework

12 Superiority, equivalence, or non-inferiority hypothesis testing framework, including which comparisons will be presented on this basis

A superiority trail aiming to compare change in disability after 52 weeks in two groups of patients with chronic low back pain, comparing an existing rehabilitation programme to an integrated rehabilitation programme. Furthermore, to compare changes in the two rehabilitation programmes on pain, pain self-efficacy, quality of life, depression and exercise capacity.

The hypotheses is, that the integrated rehabilitation programme will experience a five points larger improvement in Oswestry Disability Index compared to existing rehabilitation programme. Furthermore, the integrated rehabilitation programme will experience a larger improvement in pain, pain self-efficacy, quality of life, depression and exercise capacity compared to existing rehabilitation programme.

Statistical interim analyses and stopping guidance

13a Information on interim analyses specifying what interim analyses will be carried out and listing of time points

13b Any planned adjustment of the significance level due to interim analysis

13c Details of guidelines for stopping the trial early

An interim analyses will not be done, as none of the programmes are suspected to cause any harm. Furthermore, the timeframe of the study does not allow for interim analyses.

Timing of final analysis

14 Timing of final analysis, eg, all outcomes analyzed collectively or timing stratified by planned length of follow-up

Data from 52-week follow-up will be analyzed collectively in November 2019 (paper 3).

Data from 26-week follow-up was analyzed in May/June 2019 (paper 2). Paper 2 is under review.

Timing of outcome assessments

15 Time points at which the outcomes are measured including visit "windows"

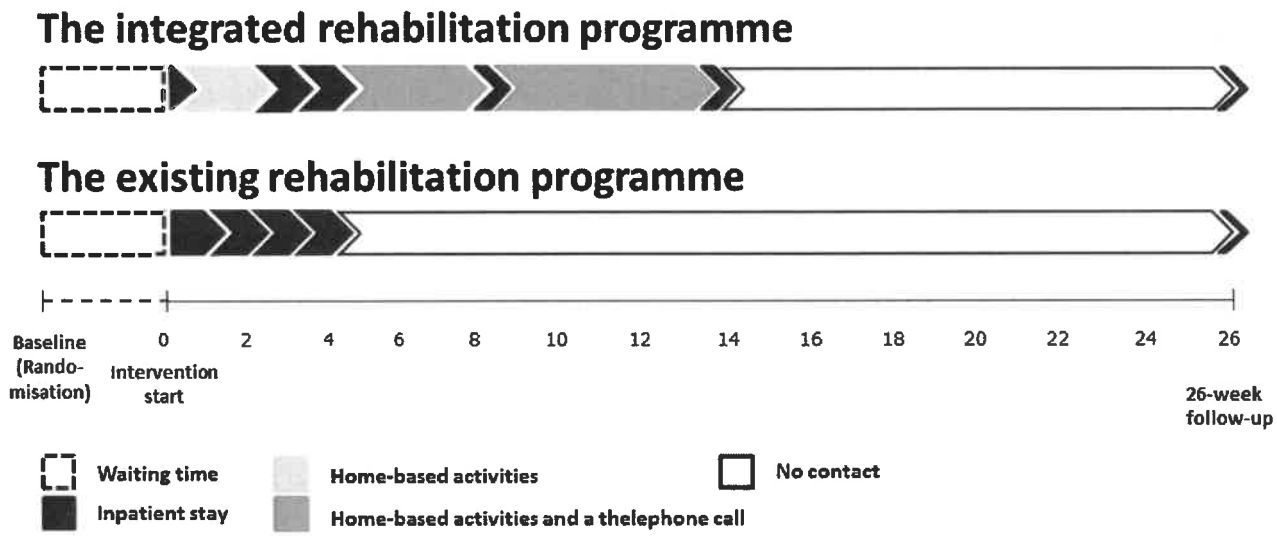


Figure 1. The existing programme and the integrated programme being compared.

The measurement time points are:

t0 = baseline/randomisation (identical in the two groups)

t1 = intervention start (identical in the two groups – existing: start 4-week inpatient + integrated: pre-assessment day)
t2 = start of 2-week inpatient (integrated)
t3 = end of 2-week inpatient (integrated)
t4 = end of 4-week inpatient (existing)
t5 = first booster session (integrated)
t6 = second booster session (integrated)
t7 = 26-week follow-up (identical in the two groups)
t8 = 52-week follow-up (identical in the two groups) (this measurement time point is not illustrated in Figure 1).
In Table 1 variables and outcomes are illustrated in relation to measurement time point.

Table 1. Variables and outcomes in relation to measurement time points.

	T0	T1	T2	T3	T4	T5	T6	T7	T8
Demographics	X								
ODI	X	X	X	X	X	X	X	X	X
NRS	X	X	X	X	X	X	X	X	X
EQ-5D	X	X						X	X
PSEQ	X	X	X	X	X	X	X	X	X
MDI	X	X		X	X			X	X
Physical activity	X							X	X
Exercise capacity		X						X	
Clinical and neurological findings		X							
Group satisfaction		X						X	

Section 4: Statistical Principles

Confidence intervals and *P* values

16 Level of statistical significance

P values ≤ 0.05 will be considered statistically significant.

17 Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled

Adjustment for multiplicity will not be done as we have chosen one primary outcome, and as we are only comparing two programmes.

18 Confidence intervals to be reported

95% CI will be used consistently across outcomes.

Adherence and protocol deviations

19a Definition of adherence to the intervention and how this is assessed including extent of exposure

In pragmatic trials there is a larger degree of flexibility due to adherence. Therefore, our primary analysis will be conducted as an intention-to-treat analysis regardless of adherence to the inpatient stay.

In a previous paper assessing the outcomes at 26-week follow-up we found that only one person didn't adhere to the protocol. Based on knowledge from this previous paper we decided not to do a per-protocol analysis in the present paper.

19b Description of how adherence to the intervention will be presented

Adherence to the intervention will be presented as number and percentages of patients attending ≥80% of the inpatient days.

19c Definition of protocol deviations for the trial

Protocol deviation is attending < 80% of the inpatient days.

19d Description of which protocol deviations will be summarized

Patients attending <80% of the inpatient days will be presented as number and percentages of patients.

Analysis populations

20 Definition of analysis populations, eg, intention to treat, per protocol, complete case, safety

Intention-to-treat analysis will be performed (by original assigned groups) regardless of the degree of adherence.

See 19a.

Section 5: Trial Population

Screening data

21 Reporting of screening data (if collected) to describe representativeness of trial sample

The period recruiting, the total number of patients assessed for eligibility, the number of patients recruited, the number of screened patients not recruited, and the reason for non-recruitment will be reported in the text and/or in the CONSORT flow diagram.

Eligibility

22 Summary of eligibility criteria

Inclusion: 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.

Exclusion: 1) severe systemic diseases (American Society of Anesthesiologists Physical Status classification system ≥ 3[14]), 2) a diagnosis of axial spondyloarthritis, 3) spinal fracture within the last three months, 4) severe osteoporosis, 5) active cancer, 6) active psychiatric pathology, 7)

pregnancy, 8) lack of fluency in Danish, and 9) minimal back-specific disability (Oswestry Disability Index score < 21[15]).

Recruitment

23 Information to be included in the CONSORT flow diagram

The CONSORT flow diagram will be used.

Withdrawal/follow-up

24a Level of withdrawal, eg, from intervention and/or from follow-up

The level of withdrawal will be presented in the CONSORT flow diagram.

24b Timing of withdrawal/lost to follow-up data

Will be presented in CONSORT flow diagram with numbers and reasons for withdrawal and/or exclusion given at each stage (before the intervention, during the intervention, 26-week follow-up or 52-week follow-up).

24c Reasons and details of how withdrawal/lost to follow-up data will be presented

Will be presented in CONSORT flow diagram with numbers and reasons for withdrawal and/or exclusion given at each stage (before the intervention, during the intervention, 26-week follow-up or 52-week follow-up).

Baseline patient characteristics (Table 1)

25a List of baseline characteristics to be summarized

Identical to Table 1 in paper 2 + in addition a column showing total data (n=165) in order to present data on the whole population.

	Patients allocated at baseline	
	Existing programme n=83	Integrated programme n=82
Gender (women) n (%)	60 (73%)	60 (72%)
Age (years)		
Mean (SD)	51 (13)	49 (13)
Range	25-84	22-72
Marital status n (%)		
Married	58 (70%)	60 (73%)
Single/widowed	25 (30%)	22 (27%)
Smokers n (%)		
Yes	28 (34%)	24 (29%)
No	55 (66%)	58 (71%)
Leg pain n (%)		
Yes	59 (71%)	65 (79%)
No	17 (21%)	12 (15%)
Don't know	7 (8%)	5 (6%)
Employment status* n (%)		
Self-supporting	16 (25%)	17 (26%)
Temporary social benefits	11 (17%)	9 (14%)

Permanent social benefits	27 (42%)	29 (45%)
Age-related pension	10 (16%)	8 (12%)
Others	0 (0%)	2 (3%)
Education level*		
Low (≤12 years)	14 (22%)	
Middle (≤16 years)	44 (69%)	10 (15%)
High (> 16 years)	6 (9%)	44 (68%)
		11 (17%)
Disability ODI (0-100)**		
Mean (SD)	43 (11)	42 (10)
Range	24-72	20-68
Back pain intensity* NRS (0-10)**		
Mean (SD)	6 (2)	6 (2)
Pain Self-efficacy PSEQ (0-60)		
Mean (SD)	27 (10)	28 (11)
Quality of life EQ-5D 5L (-0.624-1)		
Mean (SD)	0.603 (0.118)	0.567 (0.157)
Depression MDI (0-50)		
Mean (SD)	20 (11)	20 (12)
Physical activity n (%)		
Minutes spent on physical exercise during a week		
< 30	50 (60%)	42 (51%)
≥30 ≤ 120	31 (37%)	32 (39%)
> 120	2 (3%)	8 (10%)
Minutes spent on physical activity during a week		
< 30	20 (24%)	13 (16%)
≥30 ≤ 300	55 (66%)	52 (63%)
> 300	8 (10%)	17 (21%)
Hours spent sitting during 24 hours		
≥ 10	14 (17%)	9 (11%)
<10 ≥4	52 (63%)	53 (65%)
<4	17 (20%)	20 (24%)

*Due to technical issues in the database, data on employment status and education level was only available in ≈ 75% of the patients.

**Due to technical issues in the database, one patient with an ODI score of 20 was included.

***Mean back pain intensity for the last two weeks.

ODI: Oswestry Disability Index

NRS: Numerical Rating Scale

PSEQ: Pain Self-Efficacy Questionnaire

EQ-5D 5L: EuroQol-5 Domain 5-level

MDI: Major Depression Inventory

Variables, Clinical and neurological findings and outcomes that will **not** be presented:

Variables (collected as a part of usual practice)

- Who referred you?
- Have you attended a rehabilitation programme before? If yes: Where did you attend a rehabilitation programme?
- Number of children
- Support from relatives
- weekly consumption of alcohol
- Unsolved economic claims
- Satisfaction with allocation (measured at intervention start (not baseline) and can therefore be influenced by waiting time + measured at 26-week follow-up).

Clinical and neurological findings

Collected by an experienced rheumatologist at the first inpatient contact using a standardized examination protocol - data not used in the present trial.

Outcomes

- Physical activity (PROM) - due to poor quality of data revealed in paper 2
- Exercise capacity (objective measurement) - due to technical problems

25b Details of how baseline characteristics will be descriptively summarized

The included study population will be described in a table 1 without p-values (according to test for baseline differences see Michiel de Boer "Testing for baseline differences" International journal of behavioural nutrition and physical activity, 2015).
Differences in personal (sex and age) and disease characteristic (diagnosis) will be compared between patients randomized and patients refused to participate in the study.
Baseline characteristics will be descriptively summarized and presented by mean (SD), median (IQR) or number (%).

Section 6: Analysis

Outcome definitions

List and describe each primary and secondary outcome including details of:

26a specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (eg, order in which they will be tested).

Primary outcome:

- Disability

Secondary outcomes:

- Pain
- Pain self-efficacy
- Quality of life
- Depression
- Daily activity level
- Exercise capacity data were collected, but due to the poor quality of data, data will not be presented.

Furthermore, the following variables will be collected:

- Demographics (see Table 1)

26b specific measurement and units (eg, glucose control, hbA1c [mmol/mol or %])

Primary outcome:

- Disability assessed by the Oswestry Disability Index, a 10-item scale where high score reflects great disability.

Secondary outcomes:

- Pain assessed quantitatively with Numerical Rating Scale.
- Pain self-efficacy measured by The Pain Self-Efficacy Questionnaire.
- Quality of life measured by EQ-5D.
- Depression measured by Major Depression Inventory.
- Daily activity level measured by three questions (https://www.fysio.dk/nyheder/2014/Hvordan-sporger-du-ind-til-patienternes-aktivitetsniveau)
  (Due to the poor quality of data, data will not be presented).
- Exercise capacity measured by Aastrands cycle test (due to the poor quality of data, data will not be presented).

26c any calculation or transformation used to derive the outcome (eg, change from baseline, QoL score, time to event, logarithm, etc)
Outcomes will be measured as changes from baseline (=randomisation) to 52-week follow-up.

Analysis methods
27a what analysis method will be used and how the treatment effects will be presented
The analysis of the continuous outcomes will be a linear mixed model with a random intercept automatically including all available data (n=165 patients randomized).
The following measurement time point will be used: t0, t1, t7 and t8 (see *15 Time points at which the outcomes are measured including visit "windows"*).

Primary analyses: difference in change between groups from baseline to 52 week.
Additionally within-group changes will be presented.

27b any adjustment for covariates.
None

27c methods used for assumptions to be checked for statistical methods
Assumptions of the applied statistical tests will be checked by inspection of the distribution of the residuals and random intercepts.

27d details of alternative methods to be used if distributional assumptions do not hold, eg, normality, proportional hazards, etc
If distributional assumptions do not hold we will provide bootstrap 95% bias corrected confidence intervals.

27e any planned sensitivity analyses for each outcome where applicable
- Adding waiting time as a covariate in the primary analysis

- An analysis of a complete dataset with missing values imputed by the average of none-missing scores at the particular time point and by worst possible score (highest score) - this will only be done for the primary outcome.

27f any planned subgroup analyses for each outcome including how subgroups are defined

Missing data

28 Reporting and assumptions/statistical methods to handle missing data (eg, multiple imputation)

See 27e

Additional analyses

29 Details of any additional statistical analyses required, eg, complier-average causal effect analysis

Harms

30 Sufficient detail on summarizing safety data, eg, information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analyzed, ie, grade 3/4 only, incidence case analysis, intervention emergent analysis

Cases of death or adverse events (reported by the rheumatologist) will be reported.

Statistical software

31 Details of statistical packages to be used to carry out analyses

For statistical analysis, STATA (version 16) will be used.

References

32a References to be provided for nonstandard statistical methods

32b Reference to Data Management Plan

32c Reference to the Trial Master File and Statistical Master File

32d Reference to other standard operating procedures or documents to be adhered to

Appendix 8

Activity sheets describing each of the 38 clinical activities (September 2016)

Item 4 (What (procedures)), item 5 (Who provided), item 6 (How), item 8 (When and how much), and item 9 (Tailoring) from the TIDieR checklist[1] are described for each of the 38 clinical activities.

Clinical assessment

What (procedures)		**Physical assessment** Anamnesis, individual physical assessment of range of motion, strength, neurology, blood pressure, stethoscopy, registration/adjustment of medication, allergy, alcohol, and/or smoking.
Tailoring		Yes
Who provided		Rheumatologist and physiotherapist
How		Individual counselling
When and how much	Number of sessions	1
	Duration	30 minutes
	Intensity	-

What (procedures)		**Psychosocial assessment** Dialog about individual psychosocial *barriers* to and *facilitators* of functioning.
Tailoring		Yes
Who provided		Nurses and occupational therapist
How		A part of the individual nurse and occupational therapist counselling
When and how much	Number of sessions	2
	Duration	30 minutes
	Intensity	-

Motivation and change

What (procedures)		**Instruction in exercise app** Introduction to the functionalities in the exercise app.
Tailoring		No
Who provided		Physiotherapist
How		Group lecture
When and how much	Number of sessions	2
	Duration	30 minutes
	Intensity	-

What (procedures)		**Introduction to rehabilitation** Knowledge about and insight into how the body, environment and mentality influences the way we live with a disease. Introduction to tools helping them to influence body, environment, and mentality in order to make them cope with their life situation.
Tailoring		No
Who provided		Occupational therapist
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	60 minutes
	Intensity	-

What (procedures)		**Exercise theory** Theory/principles for aerobe, anaerobe/strength and mobility exercises. How exercise influences both physical and mental health.
Tailoring		No
Who provided		Physiotherapist
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	60 minutes
	Intensity	-

What (procedures)		**Introduction to mindfulness** The aim is to develop the participants' ability to be with "what is" without making any judgements or evaluations. The session works towards facilitating the participants' relation to thoughts, feelings, and bodily sensations.
Tailoring		No
Who provided		Mindfulness instructor
How		Group sessions
When and how much	Number of sessions	1-4
	Duration	45-60 minutes
	Intensity	-

What (procedures)		**Involvement of relatives** The aim is to create a common language and understanding among patients and their relatives by educating them in Sano's theoretical approach and individualised focus on treatment. The arrangement compromises knowledge on everyday life strategies, pain knowledge and management and training principles.
Tailoring		No
Who provided		Three providers from the multidisciplinary team
How		- Group session - Possibility to attend treatment sessions, counselling, lectures and diner
When and how much	Number of sessions	1 group session Unlimited possibility to visit relatives.
	Duration	150 minutes
	Intensity	-

What (procedures)		**Motivation and anchoring** How to set goals for the future focusing on how to combine everyday life with physical and mental capacity. Insight into the circle of motivation and anchoring as a useful tool in an everyday life setting.
Tailoring		No
Who provided		Nurses
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	60 minutes
	Intensity	-

What (procedures)		**The next step** How to create a satisfying and meaningful life and still accept the "pain" life brings.
Tailoring		No
Who provided		Nurses
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	45 minutes
	Intensity	-

Pain knowledge and management

What (procedures)		**Chronic pain and chronic back pain** Theory about chronic pain and chronic back pain.
Tailoring		No
Who provided		Rheumatologist
How		Group lecture and dialog
When and how much	Number of sessions	One lecture every fortnight
	Duration	60 minutes
	Intensity	-

What (procedures)		**Experiences with pain** The patients will gain insight into how pain can influence physical, mental, and social state of well-being.
Tailoring		No
Who provided		Nurses
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	45 minutes
	Intensity	-

What (procedures)		**Knowledge about pain** Understanding pain and mentality. Knowledge about terms such as stimuli, receptors, sensors, alarm system, and sensitization. Histories and metaphors making it easier to understand pain.
Tailoring		No
Who provided		Nurses
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	45 minutes
	Intensity	-

What (procedures)		**Knowledge about analgesic medicine** Introduction to the different groups of analgesic medicine including effects and side effects, in order to see analgesic medicine as a remedy to increase disability and quality of life.
Tailoring		No
Who provided		Nurses
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	45 minutes
	Intensity	-

What (procedures)		**Living with pain** Theoretic class where the patient will gain knowledge about acute and chronic pain, and gain insight into how they actively can change undesirable thoughts and behavior caused by chronic pain, and how to divert thoughts about pain. The patients will be presented to terms such as catastrophizing, stress, energy givers/energy drainers, quality of life, and accept of own situation.
Tailoring		No
Who provided		Nurses
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	60 minutes
	Intensity	-

Multidisciplinary intervention

What (procedures)		**Welcome meeting** Introduction and status.
Tailoring		No
Who provided		One provider from the multidisciplinary team
How		Group session and dialog
When and how much	Number of sessions	2-3
	Duration	30
	Intensity	-

What (procedures)		**Multidisciplinary conference** A patient-centred conference identifying individual self-directed goals and making an individual rehabilitation plan.
Tailoring		Yes
Who provided		Two-four providers from the multidisciplinary team
How		Individual counselling
When and how much	Number of sessions	1
	Duration	30 minutes
	Intensity	-

What (procedures)		**Open counselling** An individually conversation where the patient can ask questions and have his or her exercise program adjusted.
Tailoring		Yes
Who provided		Two providers from the multidisciplinary team
How		Individual counselling
When and how much	Number of sessions	5 days a week (voluntary)
	Duration	30 minutes
	Intensity	-

What (procedures)		**Midterm evaluation** Evaluation of individual self-directed goals and revision of the individual rehabilitation plan.
Tailoring		Yes
Who provided		One provider from the multidisciplinary team
How		Individual counselling
When and how much	Number of sessions	1
	Duration	30 minutes
	Intensity	-

Exercise and physical activity

What (procedures)		**Aqua gymnastic** Aerobe and anaerobe exercises as well as exercises focusing on mobility and stability/balance.
Tailoring		The exercises are chosen and adjusted based on the individual patient.
Who provided		Physiotherapist
How		Group session
When and how much	Number of sessions	Supervised: 4 sessions Non-supervised: 6 sessions
	Duration	30 minutes incl. warm-up and cool-down
	Intensity	Borg 11-15

What (procedures)		**Circuit training** Aerobe and anaerobe exercises of the whole body using elastics, weights, balls, trampoline, step benches, and exercise bikes.
Tailoring		The exercises are chosen and adjusted based on the individual patient.
Who provided		Physiotherapist
How		Group session
When and how much	Number of sessions	Supervised: 3-5 sessions Non-supervised: 6-9 sessions
	Duration	30 minutes incl. warm-up and cool-down
	Intensity	Borg 14-17

What (procedures)		**Intro electric bicycle** Outdoor introduction to electric bicycles that can be borrowed.
Tailoring		Yes
Who provided		Physiotherapist
How		Group session
When and how much	Number of sessions	1 (voluntary)
	Duration	30 minutes incl. warm-up and cool-down
	Intensity	Borg 11-15

What (procedures)		**Exercise capacity training** The focus is on increasing exercise capacity (Vo2max) using spinning bicycles and step benches.
Tailoring		The exercises are chosen and adjusted based on the individual patient.
Who provided		Physiotherapist
How		Group session
When and how much	Number of sessions	2-3
	Duration	30 minutes incl. warm-up and cool-down
	Intensity	Borg 16-17

What (procedures)		**Healthy feet** Warm up, strength- and mobility exercises with small gymnastic balls in different postures. Provide knowledge about different foot types, how to choose appropriate footwear, and how to provide adequate care for the feet.
Tailoring		No
Who provided		Physiotherapist
How		Group session
When and how much	Number of sessions	2 (individually referred)
	Duration	30 minutes
	Intensity	Borg 7-10

What (procedures)		**Closing activity** Relaxation activity and goodbye.
Tailoring		No
Who provided		Physiotherapist
How		Group session
When and how much	Number of sessions	1
	Duration	45 minutes
	Intensity	-

Individual counselling

What (procedures)		**Individual nurse counselling** The counselling will be based on the patient's experiences and challenges motivating and supporting them to empower their future.
Tailoring		Yes
Who provided		Nurses
How		Individual counselling
When and how much	Number of sessions	4-6
	Duration	30-45 minutes
	Intensity	-

What (procedures)		**Individual physiotherapy counselling** Instruction in exercise programs and continuous progression/regression of exercises.
Tailoring		Yes
Who provided		Physiotherapist
How		Individual counselling
When and how much	Number of sessions	6-9
	Duration	20-30 minutes
	Intensity	-

What (procedures)		**Individual occupational therapy counselling** Focus on habits, roles, and routines in the patient's everyday life.
Tailoring		Yes
Who provided		Occupational therapy
How		Individual counselling
When and how much	Number of sessions	4
	Duration	30-45 minutes
	Intensity	-

What (procedures)		**Individual dietary counselling** Includes e.g. weight loss or weight gain strategies, irritable bowel syndrome, food intolerances, etc.
Tailoring		Yes
Who provided		Nutritional counsellor
How		Individual counselling
When and how much	Number of sessions	2-4 (individually referred)
	Duration	45-60 minutes
	Intensity	-

What (procedures)		**Individual rheumatologic counselling** Includes e.g. disease pathology and etiology, disease management at any level, medication, physical examination, joint- or bursa-injection.
Tailoring		Yes
Who provided		Rheumatologist
How		Individual counselling
When and how much	Number of sessions	0-2 (individually referred)
	Duration	15-30 minutes
	Intensity	-

Essential activity

What (procedures)		**Activity and health** The patients will gain knowledge about and learn to understand the connection between activity and health. The patients will gain insight into how their engagement in meaningful activities in their everyday life influences their physical and mental wellbeing. The patients are introduced to the dimensions of activity and how they can use problem solving in performing everyday life activities.
Tailoring		No
Who provided		Occupational therapist
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	60 minutes
	Intensity	-

What (procedures)		**Balanced activity** Knowledge about how, in a desirable way, to organise and priorities activities and energy in everyday life situations. Knowledge about diversities in activities and discussion about how to create equilibrium between duty and inclination.
Tailoring		No
Who provided		Occupational therapist
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	60 minutes
	Intensity	-

What (procedures)		**Activity and social relations** Dialog concerning how social relations affect health and everyday life activities. The patients prepare a social activity together where their newly acquired skills on problem solving according to activities are used.
Tailoring		Yes
Who provided		Occupational therapist
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	60 minutes
	Intensity	-

What (procedures)		**Lifelong activity** How to maintain the process with gaining activities as desired.
Tailoring		No
Who provided		Occupational therapist
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	60 minutes
	Intensity	-

Activities of daily living

What (procedures)		**Sleep** Introduction to sleep related problems as for example difficulties falling asleep, unrestful sleep, or waking up early. What is a good night's sleep, how unrestful or the lack of sleep can affect physical and mental health, what can be done to obtain a better night's sleep, and the principles for a good sleeping position.
Tailoring		Yes
Who provided		Occupational therapist
How		Group lecture and dialog
When and how much	Number of sessions	1 (individually referred)
	Duration	60 minutes
	Intensity	-

What (procedures)		**House and garden** The focus is on the individual patient's disabilities with cleaning, shopping staple goods, gardening, and/or cooking.
Tailoring		Yes
Who provided		Occupational therapy
How		A workshop with a combination of theory, exchange of experience and putting it into practice.
When and how much	Number of sessions	1 (individually referred)
	Duration	60 minutes
	Intensity	-

Nutrition and weight loss

What (procedures)		**Permanent weight loss strategies** Lecture developed by the Danish Health Authority. Focus is on how to start losing weight and how to maintain the weight loss e.g. a result of diet changes.
Tailoring		No
Who provided		Physiotherapist
How		Group lecture and dialog
When and how much	Number of sessions	1 (only for patients with BMI>25)
	Duration	30 minutes
	Intensity	-

What (procedures)		**Healthy Lifestyle** Provided an introduction to macro- and micronutrients. Providing the patients with knowledge on e.g. nutrition recommendations drafted by The National Board of Health concerning e.g. fruits and vegetables, saturated fat, omega-3 fatty acids, sugar, etc.
Tailoring		No
Who provided		Nutritional counsellor
How		Group lecture and dialog
When and how much	Number of sessions	1
	Duration	60 minutes
	Intensity	-

Individual exercise

What (procedures)		**Individual exercise** Unsupervised individual exercise in accordance with physiotherapy instructions.
Tailoring		Yes
Who provided		-
How		Individual
When and how much	Number of sessions	2-3 times a day
	Duration	10-30 minutes
	Intensity	Individual

1. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ (Clinical research ed)* 2014; 348: g1687. 2014/03/13. DOI: 10.1136/bmj.g1687.

Appendix 9

Graphical depiction comparing the integrated programme and the existing programme (September 2016).

Item 3 (What (materials)), 4 (What (procedures)), 6 (How), 7 (Where) and 8 (When and how much) from the TIDieR checklist (1) are included in the graphical depiction comparing the two rehabilitation programmes. Individual counselling (except from Day 1) and individual exercise are not included in the graphical comparison as they were planned and conducted individually. Further, randomisation and measurement time points are depicted. The depiction is inspired by Perera's PaT Plot (2).

Time line	Integrated programme	Existing programme
Physical or informational materials	Participant consent Informed consent	Participant consent Informed consent
Measurements (t0)	Baseline characteristics The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire EQ-5D Major Depression Inventory Physical activity	Baseline characteristics The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire EQ-5D Major Depression Inventory Physical activity
Randomisation		
Physical or informational materials	Welcome pamphlet describing the clinical activities.	Welcome pamphlet describing the clinical activities.
Measurements (t1)	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire EQ-5D Major Depression Inventory Physical activity Aerobic exercise capacity test	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire EQ-5D Major Depression Inventory Physical activity Aerobic exercise capacity test
Physical or informational materials	Pamphlet containing individualized preparation material focusing on facilitation of goal setting as well as physical and mental preparation before the next inpatient stay.	
Day 1	Welcome meeting Physical assessment Psychosocial assessment Individual nurse counselling Individual occupational therapy counselling Individual physiotherapy counselling	Welcome meeting Physical assessment Psychosocial assessment Individual nurse counselling Individual occupational therapy counselling Individual physiotherapy counselling

	Instruction in exercise app	Instruction in exercise app
Day 2	Home-based activities	Open counselling Multidisciplinary conference Introduction to rehabilitation Chronic pain and chronic back pain Aqua gymnastic
Day 3	Home-based activities	Open counselling Experiences with pain Circuit training
Day 4	Home-based activities	Open counselling Activity and health Exercise theory Aqua gymnastic Circuit training
Day 5	Home-based activities	Open counselling Intro electric bicycle Mindfulness Aqua gymnastic Exercise capacity training
Day 6	Home-based activities	Home
Day 7	Home-based activities	Home
Day 8	Home-based activities	Open counselling Knowledge about pain Healthy feet Circuit training
Day 9	Home-based activities	Open counselling Knowledge about analgesic medicine Aqua gymnastic Circuit training
Day 10	Home-based activities	Open counselling Sleep Mindfulness Circuit training Aqua gymnastic
Day 11	Home-based activities	Open counselling Balanced activity Aqua gymnastic Circuit training
Day 12	Home-based activities	Open counselling Midterm evaluation Weight loss that lasts Exercise capacity training
Day 13	Home-based activities	Home
Day 14	Home-based activities	Home
Measurements (t2)	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire	
Day 15	Home-based activities	Open counselling

		Instruction in exercise app Aqua gymnastic Circuit training
Day 16	Multidisciplinary conference Introduction to rehabilitation Chronic pain and chronic back pain Aqua gymnastic	Open counselling House and garden Chronic pain and chronic back pain Aqua gymnastic Circuit training
Day 17	Open counselling Experiences with pain Sleep Circuit training Aqua gymnastic	Open counselling Mindfulness Healthy lifestyle Circuit training
Day 18	Open counselling Exercise theory Activity and health Weight loss that lasts Circuit training Aqua gymnastic	Open counselling Activity and social relations Circuit training Aqua gymnastic
Day 19	Open counselling Intro electric bicycle Mindfulness Exercise capacity training Aqua gymnastic	Open counselling Living with pain Exercise capacity training
Day 20	Home-based activities	Home
Day 21	Home-based activities	Home
Day 22	Open counselling Instruction in exercise app Knowledge about pain Healthy feet Circuit training Involvement of relatives	Open counselling Healthy feet Circuit training Aqua gymnastic Involvement of relatives
Day 23	Open counselling Knowledge about analgesic medicine Chronic pain and chronic back pain Aqua gymnastic Circuit training	Open counselling Motivation and anchoring Aqua gymnastic Circuit training
Day 24	Open counselling Mindfulness Sleep Circuit training	Open counselling Lifelong activity Mindfulness Circuit training
Day 25	Open counselling Balanced activity Aqua gymnastic Circuit training	Open counselling Circuit training
Day 26	Open counselling Living with pain Aqua gymnastic Exercise capacity training	Open counselling Circuit training Aqua gymnastic

Measurements (t3)	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire Major Depression Inventory	
Measurements (t4)		The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire Major Depression Inventory
Home-based activities	4 weeks of home-based activities	
		End of existing programme
Modes of delivery	One phone call initiated by the multidisciplinary team. Opportunity to contact the multidisciplinary team once via exercise app (patient initiated).	Opportunity to contact the multidisciplinary team twice in three months after discharge via exercise app (patient initiated).
Measurements (t5)	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire	
Day 1 Booster session 1	Open counselling Midterm evaluation Motivation and anchoring House and garden Activity and social relations Aqua gymnastic Circuit training	
Day 2 Booster session 1	Open counselling Mindfulness Healthy Lifestyle Circuit training Aqua gymnastic	
Home-based activities	6 weeks of home-based activities	
Modes of delivery	One phone call initiated by the multidisciplinary team. Opportunity to contact the multidisciplinary team once via exercise app (patient initiated).	
Measurements (t6)	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire	
Day 1 Booster session 2	Open counselling Welcome meeting Mindfulness Aqua gymnastic Circuit training	

Day 2 Booster session 2	Open counselling Lifelong activity Aqua gymnastic	
	End of integrated programme	
Measurements (t7)	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire EQ-5D Major Depression Inventory Physical activity Exercise capacity test	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire EQ-5D Major Depression Inventory Physical activity Exercise capacity test
6-month follow up visit	Welcome meeting Individual counselling The next step Closing activity	Welcome meeting Individual counselling The next step Closing activity
Measurements (t8)	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire EQ-5D Major Depression Inventory Physical activity	The Oswestry Disability Index Numerical Rating Scale (Pain) Pain Self-Efficacy Questionnaire EQ-5D Major Depression Inventory Physical activity

1. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ (Clinical research ed). 2014;348:g1687.
2. Perera R, Heneghan C, Yudkin P. Graphical method for depicting randomised trials of complex interventions. BMJ (Clinical research ed). 2007;334(7585):127-9.

Appendix 10

Examples of process findings from process research question 1 and 2 (not an exhaustive list).

Date	Awareness	Action
September 2016	Interview with the internal pilot group (attending their 2-week inpatient stay): - Didn't have a phone call before the inpatient stay - It was not stated explicit in the invitation, that the pre-admission day was a whole day - A place to rest on the pre-admission day was requested - A single patient failed to appear on the pre-admission day due to lack of invitation	- Administrative changes - Change of text in the invitation - Two rooms are redecorated for the purpose of rest - Administrative changes
October 2016	The exercise capacity test causes practical and technical difficulties.	Theoretical and practical teaching in conducting the exercise capacity test.
November 2016	Interview with the internal pilot group (attending their initial booster session): - Confusion about where to sit in the dining room; request a reserved table - 3 patients in a group is too few	
November 2016	Some of the integrated programmes ends up with small groups due to postponements.	Overbooking of the integrated programme (like in the existing programme).
November 2016	Some patient's postpone their inpatient stay due to work, private problems or health status after randomization.	Waiting time is not only due to the organisation, but can be prolonged voluntary by the patient. This awareness led to process research question 6.
November 2016	The providers point out that many patients are not using the pamphlet.	The providers that developed the pamphlet presents it and its aim on a meeting for all providers.

November 2016	Lack of resources in the administration staff to handle the inclusion in the RCT.	Resources are allocated to employ a research assistant 5 hours/week.
January 2017	Interview with the internal pilot group (attending their second booster session): - Positive about the pamphlet - Positive about the phone call - Very positive about the booster sessions (a carrot><a whip)	
March 2017	Interview with the internal pilot group (attending 26-week follow up visit): - Request a programme for the inpatient stay a few days in advance of the inpatient stay - Request a farewell dinner identical to patients in the existing programme - Satisfied with the programme on the 26-week follow up visit, and in general satisfied with the integrated programme.	- The administrative and management staff arrange this - The chef arrange this
April 2017	Many patients are not able to perform the exercise capacity test due to practical or technical problems.	An exercise physiologist is invited to teach the physiotherapist on exercise capacity and test of exercise capacity.
May 2017	Lack of and different information in the 26-week follow up visit invitation.	The invitations are revised and standardised by the stakeholders.
June 2017	A group of patients attending the integrated programme articulates that being four patients in a group is too few.	The booking schedule for 2018 is revised in order to book fewer integrated programmes, and thereby increase the number of patients in each group.
September 2017	Employment of a psychologist.	
November 2017	Some of the providers point out that there is confusion about the pamphlet. Who is handing it out, and who informs the patients about how to use it.	Meeting with a representative from the physiotherapists, nurses and occupational therapist. Meeting with all providers where they are informed about the aim of the pamphlet and how to use it. It is decided that the physiotherapists will

		hand it out as a part of their first contact. Further, it is decided that the person in charge of the round off on the pre-admission day, will instruct the patients in the pamphlet.
November 2017	Providers inform that the phone calls between the booster sessions are often forgotten or made few days before the patient's inpatient stay (not in the middle of the home phase as planned).	A provider is pointed out as responsible for reminding colleagues about booking the phone call in their calender.
November 2017	Providers inform that the result of some exercise capacity test is not registered in the database.	Electronic health records are searched to find the information retrospectively.
November 2017	The pulse rate belts linked to the exercise bikes do not work.	A representative from the firm delivering the exercise bikes assess the problem.
January 2018	Interview with a group of patients in the integrated programme: - Suggests that they are offered a status conversation at the end of the 2-week inpatient stay. - Suggestions about a guided tour in the house on the pre-admission day.	 - This should have been implemented from the RCT start but for some reason it has not been. In the future, this status conversation will be implemented. - The program on the pre-admission day does not allow time for the requested guided tour .
February 2018	Interview with a group of patients in the integrated programme: - Their program is not booked properly, meaning that they do not have enough weeks between the booster sessions. - They request a reserved table for their group in the dining room as they are confused about where to sit - Troubles with double booking of clinical activities - Non-supervised circuit training was	Stakeholders go through procedures to avoid the identified problems in the future.

	scheduled before the supervised circuit training	
Marts 2018	A group of patients in the integrated programme tells that it is difficult to remember the exercises in the non-supervised circuit training when attending the booster sessions.	A physiotherapist is attending the first 15 minutes of the non-supervised circuit training in order to refresh the exercises.
April 2018	The hot water pool is defect.	In the future patients are transported by bus to a public swimming pool once a week for supervised exercises.
August 2018	The exercise bikes are moved from the basement to first floor.	Now the pulse rate belts seems to work sufficiently.
September 2018	The exercise app is out of order.	The problem lasts for approximately 2 months.
October 2018	A representative from the firm delivering the exercise bikes calibrates the bikes and concludes that they have not worked sufficiently.	Taken all the problems with the exercise capacity test into account, it is decided to exclude data from the exercise capacity test from the statistical analyses.