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Dosage of pain rehabilitation programmes for patients with chronic musculoskeletal pain: a non-inferiority randomised controlled trial

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ABSTRACT

Purpose: To analyse the effects of interdisciplinary pain rehabilitation programmes with different dosages; care as usual versus short form.

Methods: A single blinded, two armed, randomised controlled trial, with non-inferiority design was performed. All patients with chronic musculoskeletal pain referred to an outpatient multidisciplinary pain rehabilitation programme were eligible for this study. Only dosage differed, content was similar. The difference on Pain Disability Index was the primary outcome measure. Four points difference on Pain Disability Index was applied as a non-inferiority margin. Treatment effects within groups were expressed in standardised mean difference and effect sizes were calculated between the groups.

Results: Because care as usual was frequently extended, the difference in dosage between groups was limited. The study was stopped prematurely because of an a-priori stopping rule. Interim analyses are presented. Both groups (care as usual $n = 58$, short form $n = 54$) improved significantly (mean Pain Disability Index change care as usual: -10.8; short form: -8.3). Mean difference between groups was 2.5 points (95% confidence interval was -2.2 to 7.3). Effect size between groups was 0.2.

Conclusions: The 95% confidence interval for the difference in mean pain disability reduction exceeded the upper limit of the non-inferiority margin. The results of the primary analyses of this trial are, therefore, inconclusive. Ancillary analyses revealed that programme dosage was not associated with differences in the disability outcomes.

➤ **IMPLICATIONS FOR REHABILITATION**

- Optimum dosage of interdisciplinary pain rehabilitation programs is unknown and scarcely studied. This study is the first to analyse dosage as primary aim.
- Although results are inconclusive, they also suggest that differences in dosage may not automatically lead to differences in effects.
- Further research is needed to analyse what dosage works for whom; to detect optimum effective and cost-effective dosage of pain rehabilitation programmes.

Introduction

Multidisciplinary pain rehabilitation programmes are recommended for the patients with chronic low back pain [1]. Pain rehabilitation programs aim to reduce disability, distress, and use of health care services by means of education regarding physical, psychological, and practical techniques to improve function, work participation and health related quality of life [2]. Multidisciplinary programmes have shown effectiveness for patients with chronic musculoskeletal pain [1,3,4].

Across the pain rehabilitation centres nationally and internationally, there is much diversity in content and dosage of pain rehabilitation programs. Health care systems aim for the best treatments based on available evidence. However, there is paucity of evidence about the influence of dose on effects of these programs. In a recent systematic review [5], no randomised controlled trials were identified

that were designed to analyse effects of differences in dose variables on outcome of pain rehabilitation programs. Additionally, no studies have been identified whose primary objective was to analyse the association between dose and effect of pain rehabilitation program.

If optimal dosage is known, this may benefit patients and could reduce direct or indirect costs. If similar effects are achieved with a shorter program, this could lead to an earlier reduction of disability, regaining quality of life, and participation in daily life happening sooner. Shorter programmes may also minimise direct and indirect costs associated with pain rehabilitation program. Employers could also benefit from the earlier return to work for patients with work productivity loss, rehabilitation centres can reduce waiting lists and overall it can improve efficiency of care. Additionally, shorter programmes are also attractive for health care insurers and society as a whole because of the reduction of direct and indirect costs.

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The aim of this study was to analyse the differences in effects of pain rehabilitation programs with different dosages: care as usual and short form in a non-inferiority design. Because large pain rehabilitation program dosage variations exist, without evidence that higher dosage leads to better results, we hypothesised that short form will be non-inferior to care as usual in an outpatient pain rehabilitation setting.

Methods

Design

The study was a single blinded, two armed, randomised controlled trial, with a non-inferiority design [6]. The study took place at the University Medical Centre Groningen, Department of Rehabilitation Medicine, Centre for Rehabilitation, location Beatrixoord Haren. The Medical Ethics Committee of the University Medical Centre Groningen approved the study protocol (NL30094.042.11). Trial registration: international clinical trials registry platform of World Health Organization (Trial ID = NTR3385).

CONSORT guidelines for reporting noninferiority and equivalence randomized trials were used.

Operational definitions

Dosage contains both duration of the programme and number of contact hours. Duration was defined as the total length of pain rehabilitation program and is expressed in weeks. Contact hours were defined as the total amount of hours that a patient spends with therapist(s) during the program.

Participants

All patients with chronic musculoskeletal pain referred to an outpatient pain rehabilitation program at the Centre for Rehabilitation, University Medical Center Groningen, between September 2011 and October 2013 were potential participants in this study. This centre provides pain rehabilitation programs with a duration of 8, 12, 16 or 20 weeks. Patients were eligible for the study when: (1) they were admitted for a 12, 16 or 20 week pain rehabilitation program; (2) they had chronic musculoskeletal pain for more than three months without a specific pathological care as usual se; (3) they experienced chronic musculoskeletal pain induced disability; (4) social and psychological factors were assumed to be relevant in maintaining chronic musculoskeletal pain induced disability [2]; (5) they were willing to stop other treatments for chronic musculoskeletal pain during pain rehabilitation program (except pain medication); (6) they were 18 years or older; (7) they were motivated to participate in pain rehabilitation program and (8) they were willing to participate in the study and signed an informed consent. Patients were excluded when they: (1) were referred to the 8 week pain rehabilitation program; (2) were unable to understand the Dutch language; (3) had comorbidities such as heart failure, rheumatoid arthritis, or psychiatric disorders preventing a pain rehabilitation program.

Interventions

Common features of care as usual and short form

The objectives of care as usual and short form were the same and the content was similar; both treatments were outpatient, interdisciplinary pain rehabilitation programs aimed to decrease chronic musculoskeletal pain related disability, optimise participation, and increase the quality of life. Pain rehabilitation program is intended to coach patients to self-manage their pain and disability. The rehabilitation team consisted of rehabilitation physicians, occupational therapists, physiotherapists, and psychologists. Pain rehabilitation program was based on cognitive behavioural principles, and consisted pain education, for example regarding differences between acute and chronic pain. Patients were counselled to reflect on their pain management strategies (avoiding pain) and how these strategies could be changed into other management strategies (pain coping, alternating physical activity and rest and gradually increasing activities). Each patient sets individual treatment goals. The rehabilitation physicians were responsible for the medical diagnosis, interventions (if any), pain education, reduction of pain medication, and coordinated the overall treatment plan. Physiotherapists applied exercise programmes and sports activities to improve patients' confidence in movement and reduce pain-related fear, improve activity levels, and physical functioning. Occupational therapists assessed current activities and patterns in daily living and educated patients how activities could be changed into healthy activity levels (including work participation) and patterns. Psychologists coached patients in understanding and dealing with the social and emotional impact of pain in daily life, pain beliefs, barriers for behaviour change, and coached patients how to cope with pain.

After the rehabilitation physician considered a patient to be eligible for pain rehabilitation program, the patient was invited for an intake procedure, consisting of an interview by the rehabilitation team (an occupational therapist, a physiotherapist and a psychologist) and a questionnaire set [7]. The interviews were aimed at admitting a patient to the program, and were used to develop a treatment plan. If the patient was admitted to the program, the patient's team determined the required duration of 8, 12, 16 or 20 weeks based on the assessment of the complexity of the physical, social and personal situation of the patient, motivation, and ability to change behaviour. The team that determined treatment duration consisted of professionals with on average 9 years of experience in pain rehabilitation. The program consisted of occupational therapy sessions lasting 30 min, two times a week, physiotherapy sessions lasting 30 to 60 min, two times a week, and psychology sessions lasting 60 min, once a week. The session frequency of occupational therapy and physiotherapy was reduced to once a week, and the psychology sessions were reduced to once every 2 weeks, thereby reducing contact hours by 50%. All sessions were delivered in an individual setting. For clinical reasons, the duration in weeks could be adapted (extended or shortened) in care as usual and in short form, depending on the progression of the patient. Duration could be extended when additional coaching was needed to decrease disability. Duration was shortened when treatment goals were achieved earlier than expected, when the patient demonstrated continued lack of progress, or when the patient stopped the treatment, because it did not match the patient's expectations or for reasons not related to the programme (for instance holidays). Extending or shortening the duration was based on agreement between the patient and the team and decided by the rehabilitation physician. Reasons for extending or shortening were registered.

The difference between care as usual and short form was the duration (in weeks) and contact hours of pain rehabilitation program proposed to the patients after the randomisation procedure. Patients allocated to the care as usual group received 12, 16 or 20 weeks of pain rehabilitation program as proposed after the intake procedure. Patients allocated to the short form group received a pain rehabilitation program that was 4 weeks shorter than proposed (which will result in approximately 10 contact hours less on average). Thus, patients in short form received 4 weeks/10 contact hours less than proposed after intake.

Outcomes

The primary outcome variable was the difference in self-reported disability assessed at baseline (T0) and 1–3 weeks after discharge (T1) with the pain disability index (PDI) [8]. The questionnaire consists of seven items related to work, leisure and activities of daily life. Each item is scored on an 11-point scale (0 indicating no disability and 10 indicating maximum disability). The total scale ranges from 0 to 70. The PDI has been validated in different patient groups [9]. Test–retest reliability is high (ICC = 0.91) [10]. Minimal Clinically Important Change of PDI is 8.5 points for subscale "self-care" and 9.5 points for subscale "complaints" [11].

The secondary outcome variable, quality of life, was measured with the Euroqol 5D-5L [12] (EQ5D-5L; scale range −0.329 to 1.000) [13]. The EQ-5D-5L assesses five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) of health on a 5-point scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The overall health is assessed on a 0–100 visual analogue scale of 20 cm (EQ-5D-VAS). A higher score indicates a better overall state of health. The minimal clinically important difference was 10.5 points for the EQ-5D VAS and 0.03 points for the five dimensions of the EQ-5D-3L [14]. The EQ-5D-5L version is based on the EQ-5D-3L version. The 5 L version demonstrates improved discriminatory power [15], but the minimal clinically important difference for this version has not yet been examined.

Patient characteristics gender, age, marital status, educational level, work status, and welfare status, as well as pain status (location, pain duration and worst and average pain in the last week) were assessed at baseline. PDI and EQ-5D-5L were assessed at baseline (T0), 1–3 weeks after program completion (T1) and at 3 months and 1 year. This paper reports short term results (T1).

Sample size

Sample size was calculated using the group sequential non-inferiority criterion. The standard deviation (SD) on PDI scores in care as usual was 11. The non-inferiority margin was calculated as 40% of the mean change on PDI scores in care as usual, which was 10 points, and thus the non-inferiority margin was set at 4 points. For group sequential non-inferiority design, an overall alpha of 0.05 and power of 0.8 was used. Using Power Analyse and Sample Size, version 11 software, these data gave an estimation of 124 patients needed per arm and 248 patients in total. Including 10% drop-outs, 276 patients should be included for the study.

Randomisation

After determination of program duration by the team and after obtainment of informed consent, patients were sequentially and randomly assigned to the two groups by an independent person. Patients were stratified on work status (paid work or unpaid/no work), resulting in two strata. For each stratum, blocks of six were used. Randomisation was generated by using a computer random generator. Sequentially numbered, sealed, opaque envelopes were used for each stratum.

Blinding

Patients were blinded for allocation. Before inclusion, they were informed about the duration of care as usual, which could be 8, 12, 16 or 20 weeks. It was explained to patients that a duration was proposed by the team based on the assessment results. Furthermore, they were informed about the experiment of four weeks shortened duration. They were unaware of the treatment duration they were supposed to receive in care as usual, and, therefore, they were blinded for allocation to care as usual or short form. Patients were an outcome assessor for outcome measurements since they filled in the PDI and other questionnaires. They were blinded for T0 scores. Clinicians could not be blinded for intervention for the 20 weeks duration because this part only exists in the care as usual group.

Analyses

An interim analysis was planned halfway the inclusion period. This would enable us to recalculate the a priori sample size based on trial data, as opposed to assumptions (a priori). Additionally, based on a-priori stopping rules, it was decided that the trial would be stopped if more than 25% of the pain rehabilitation programs in the short form were extended or if the decrease in means on PDI was ≥4 points larger in care as usual compared to care as usual short form. Differences in mean PDI scores were tested by a one-sided t-test. In consultation with a statistician, it was decided a priori to split the alpha of 0.05 in 0.005 for the interim analysis, and 0.045 for final analyses. Because the study was stopped preliminarily, however, only one analysis was performed for which we used a two-sided 95% confidence interval (CI) approach.

Distribution of variables was assessed for normality. Based on data distribution appropriate parametric or non-parametric statistics were used.

Means and SD's of primary outcome are presented for care as usual and short form group. Statistical analyses included intention to treat analyses for primary outcomes. A CI approach was used to interpret non-inferiority (Figure 1). In the intention to treat analyses an independent sample t-test was used to analyse differences in changes between the groups regarding PDI and EQ-5D-5L scores. Based on these results 2-sided 95% CIs were calculated. Non-inferiority was established when the upper or lower limit of the 95%CI of the mean difference would not exceed the non-inferiority limits of 0 and 4 (Figure 1). Treatment effects within groups were expressed in standardised mean difference (SMD): (mean_{change}/SD_{change}). Effect sizes (ES) were calculated between groups ($\text{mean}_{change\ intervention\ group}$ − $\text{mean}_{change\ control\ group}$)/ SD_{Pooled} [16]. Interpretation of SMD and ES: <0.10 no effect; 0.10–0.30 little effect; 0.30–0.50 moderate effect; 0.50–0.80 large effect; >0.80 very large effect [17].

Ancillary analyses

Because the duration of the programs was similar between groups, a regression analysis was performed to analyse predictors of results, a per protocol analysis. The dependent variable was change in disability (PDI T1-T0). Independent variables were: PDI baseline, pain rehabilitation program duration (weeks) and contact hours, gender, average pain at baseline and interaction term of gender and duration (weeks). Residuals were checked for normal distribution. Because in some patients the program was shortened and in some the program was extended, we explored differences in baseline characteristics and trial results between patients with a shortened program, with a program as planned and patients with an extended program using Chi-square analyses and ANOVA, and regression analyses.

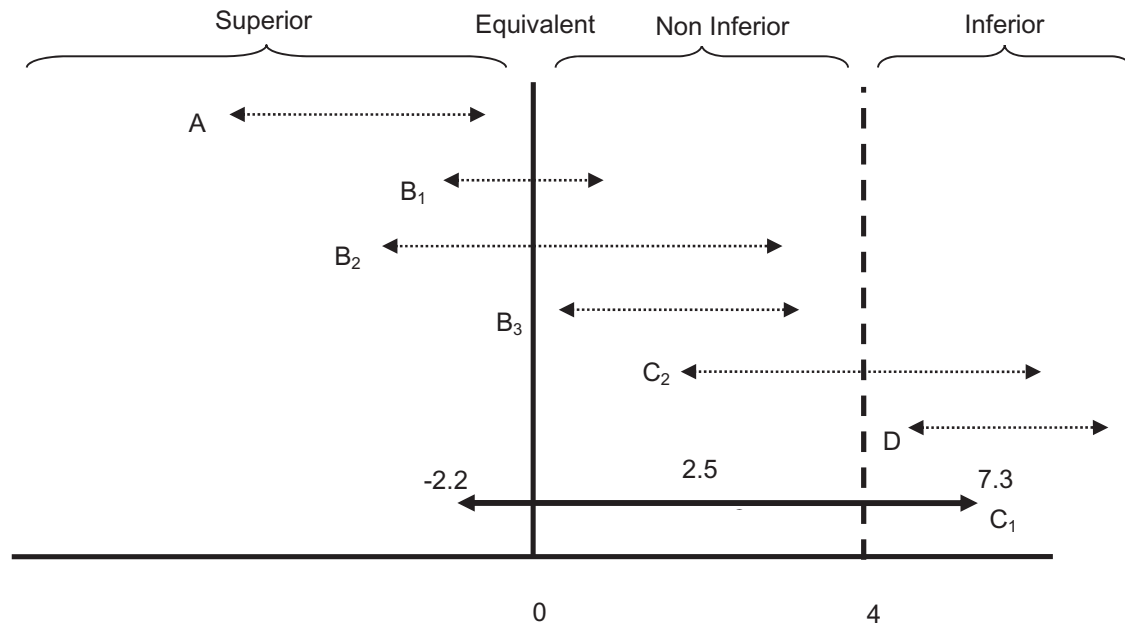All statistical analyses were performed in SPSS software version 22.

Figure 1. Illustration of the phenomenon of non-inferiority testing. The dotted double sided arrows represent the theoretical widths of the Confidence Intervals (CI) of the differences in means between the experimental group and control group. If the CI lies left of 0: (A) the experimental group is superior to the control group. If CI lies left of 4 (B_1, B_2, B_3) the experimental group is non-inferior. If CI includes 4 (C_2) non-inferiority is inconclusive. If CI lies is right to four the experimental group is inferior (D). The results of the current study resulted in solid double sided arrow C_1 with 95% confidence intervals for −2.2 to 7.3: which means non-inferiority is inconclusive.

Results

Patient characteristics and trial flow

Between September 2011 and October 2013, 694 patients were admitted. A total of 257 patients (37%) were eligible for this study and signed an informed consent. Reasons of patients for non-participation were for example: misunderstandings regarding planning, trial participation was of low priority and, consequently, patients forgot to sign the informed consent, and unwillingness to participate in the trial. Interim analyses revealed that in 36% of the patients in short form was extended and 24% in care as usual. Based on the *a priori* stopping rules, the study was stopped immediately after the interim analyses. At that point, $n = 201$ ($n = 102$ care as usual, $n = 99$ care as usual short form) patients had been randomised (Figure 2). In accordance with the rules of the METC, 30 patients who were enrolled in the trial were given the possibility to receive the admitted treatment duration and were excluded from analyses. In total 153 patients completed the program, of which $n = 81$ in care as usual and $n = 72$ in care as usual short form. Analyses were performed for patients with complete datasets: $n = 58$ in care as usual and 54 in care as usual short form. The majority of patients experienced pain for more than one year at baseline. The most prevalent diagnoses were chronic back pain (42%), chronic neck pain (19%), widespread pain (9%) and fibromyalgia (7%). Some patients reported several pain sites. Patients who completed the study differed significantly on work status and welfare status, compared to those who did not complete the study (Table 1).

Main outcomes

The reduction of PDI scores was 2.5 points larger in the care as usual group compared to the short form group (Figure 1). The mean difference of 2.5 points lies within the non-inferiority margin from 0.0 to 4.0. Because the CI of this difference exceeded the upper and lower limit of the non-inferiority margin, the results were inconclusive.

After excluding the drop-outs, in 67% of the cases, pain rehabilitation programs were delivered as planned or shorter, and in 33% of the cases pain rehabilitation programs were extended (Table 2: short form 22%; care as usual 12%). Differences in dosage between shortened, as planned, and extended programs were non-significant ($p = 0.066$). Reasons for extending were for example: changes in the behaviour or situation of the patient, return to work assistance needed more support and/or more time than anticipated, the patient case was more complex than estimated a priory, and treatment logistics.

Both groups improved significantly over time. SMD and ES for PDI and EQ5D scores are presented in Table 3. Differences in results were not significant ($p > 0.05$) between groups for both outcome measures.

Ancillary analyses

Dosage or any of the other variables did not significantly contribute to the regression model with response variable change in PDI (results not presented). The mean duration of the program for the group with a program as planned was 10.0 (SD 3.8) weeks. The mean number of contact hours was 27.1 (SD 9.7). For the extended group the mean duration was 15.0 (SD 3.3) weeks, and 39.2 (SD 8.9) contact hours (Table 4). SMD of PDI of the group with a program as planned was 0.9; ES of the extended subgroup was 0.6. Differences between groups in baseline characteristics (duration of program, shortened, as planned, and extended) were insignificant, and none of the baseline variables contributed significantly to a regression model with response variable change duration (planned versus shortened, planned versus extended) (Table 5).

Adverse events

No trial related adverse events were reported.

Enrollment

Assessed for eligibility
(n=257)

Excluded (n=56)
- Not meeting inclusion criteria (n=43)
- Excluded because stop trial (n=13)

Randomised (n=201)

Allocation

Allocated to care as usual (n=102)
- Received allocated intervention (n= 81)
- No discharge measurement (n= 5)
  Patient declined to start (n=4)
  Early drop-out (n=1)
- Excluded: premature stop trial (n=16)

Allocated to short form (n=99)
- Received allocated intervention (n=72)
- No discharge measurement (n=12)
  Administrative error (n=5)
  Patient declined to start (n=2)
  Early drop-out (n=5)
- Excluded: premature stop trial (n=14)
- Declined to participate in trial (n=1)

Analysis

Analysed (n= 81)
Drop out (n=22)

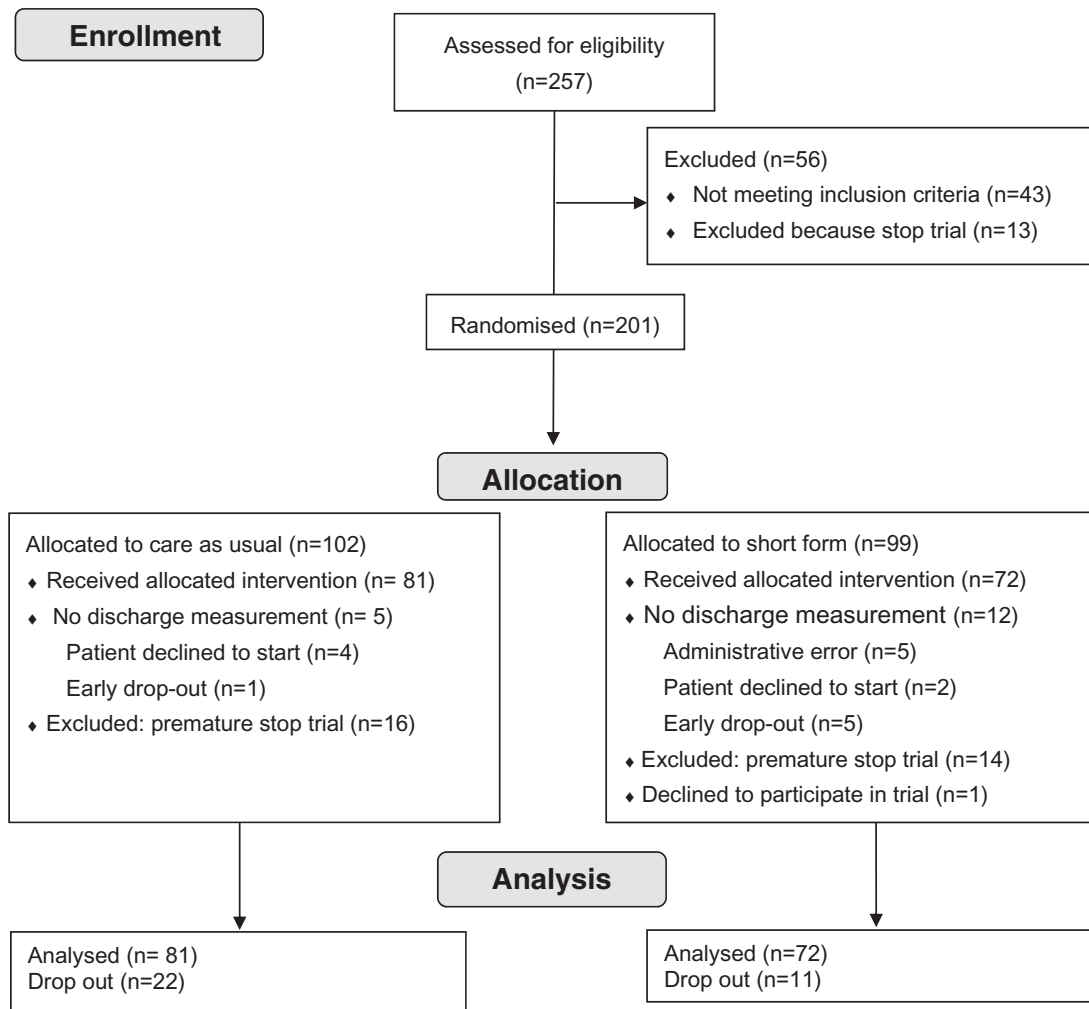Analysed (n=72)
Drop out (n=11)

Figure 2. Flow diagram.

Discussion

Results of this study were based on interim analyses because of preliminary termination and should be interpreted with care. The statistical analyses showed a mean difference in PDI change between groups of 2.5 with CI from −2.2 to 7.3, which means that the result of this non-inferiority trial was inconclusive. Within both groups, short term ES were moderate to large for the outcome measures disability and quality of life. In 25% of all cases the duration of pain rehabilitation program could be reduced.

Because of extension of pain rehabilitation program in patients randomised to short form and a limited sample size, this study was not able to detect the differences in dosage or effect between the two groups. The results could imply that shortening duration may be considered in some cases without loss of short term results. A lower dosage may benefit patients and other stakeholders. However, the duration of 26% of all programs (36% within short form and 17% within care as usual) was extended to achieve a desired outcome. Extending (and shortening) of the program was always agreed upon by the patients and the team and was a result of a goal shift between baseline and later during progression of the program. In our study, it was not possible to identify characteristics of patients whose programs were extended or shortened, and thus to plan a correct dosage at the start. This topic should be subject to further investigation. The results of the extended subgroup were similar to those of the as planned group, indicating on the one hand that extension of treatment might not be a solution to

improve treatment outcome, while on the other hand this can also be interpreted positively: results might not have been achieved without an extension. An in-depth study design with multiple interim measurements would be recommended for further analyses on this issue. Significant differences in baseline characteristics between completers and drop-outs may be assumed to be caused by differences in motivation of patients with disability compensation to complete treatment. However, characteristics of dropouts have not been a subject of this study. It is unknown whether this has systematically influenced the results of this study.

Because this trial is the first of its kind analysing dosage of pain rehabilitation, the results of this trial cannot be compared to other pain rehabilitation trials with similar designs. Patient characteristics such as pain disability, pain intensity, pain duration, and gender distribution, appear similar to other pain rehabilitation program trials, both in the Netherlands and internationally [5], and regular clinical secondary and tertiary rehabilitation programmes in the Netherlands. Dosage of pain rehabilitation program in this study was "midrange" when compared to dosage reported in other studies [18]. The results of this study stress the relevance of further dosage studies in different settings [5]. One of the main challenges expressed in pain rehabilitation is the issue of "what works for whom." We suggest adding another challenge: "how much works for whom?" Within pain rehabilitation, this may apply to the multidisciplinary programme as a whole, but also to its components. This question may open a new line of

Table 1. Baseline characteristics of participants in care as usual and short form and participants who completed the study and those who did not.

	Care as usual n = 81		Short form n = 72		Completers n = 120		Drop-outs n = 33	
	Mean n	SD %	Mean n	SD %	Median n	IQR %	Median n	IQR %
Age (years) (n = 153)	43.8	12.4	44.1	11.9	44.6	33.6–52.3	47.4	40.4–54.9
Average pain last week (n = 153)	6.5	1.6	6.9	1.6	7.0	6–8	7.0	5.0–8.0
Worst pain last week* (n = 153)	7.8	1.6	8.3	1.3	8.0	7–9	8.0	7–9
Gender (% female) (n = 153)	45	55.6	49	68.1	79	66	15	45
Duration of pain (n = 131)								
3 months to 1 year	15	23.1	20	30.3	27	25.7	8	30.8
>1 year	50	76.9	46	69.7	78	7.3	18	69.2
Assigned treatment duration (weeks) (n = 153)								
8	0	0.0	26	36.1	23	19.2	3	9.1
12	37	45.7	45	62.5	66	55.0	16	48.5
16	41	50.6	1	1.4	30	25.0	12	36.4
20	3	3.7	0	0.0	1	0.8	2	6.1
Marital status (n = 132)								
Single	9	13.6	11	16.7	16	15.2	4	14.8
Married/living (apart) together	53	80.3	47	71.2	77	73.3	23	85.2
Otherwise	4	6.1	8	12.1	12	11.4	0	0.0
Education (n = 136)								
No or low education	20	29.4	13	19.1	25	22.9	8	29.6
Middle education	30	44.1	34	50.0	51	46.8	13	48.1
High education	18	26.5	21	30.9	33	30.3	6	22.2
Work status** (n = 135)								
Employed, fulltime	19	27.5	20	30.3	34	31.8	5	17.9
Employed, part-time	22	31.9	18	27.3	36	33.6	4	14.3
Houseman/-wife	9	13.0	8	12.1	9	8.4	8	28.6
Unemployed	8	11.6	8	12.1	12	11.2	4	14.3
Otherwise	11	15.9	12	18.2	16	15.0	7	25.0
Benefit status** (n = 135)								
Not working and no benefit status	25	36.8	23	34.3	43	40.2	5	17.9
Partial sick leave/disability pension	30	44.1	30	44.8	40	37.4	20	71.4
Full sick leave/disability pension	6	8.8	9	13.4	14	13.1	1	3.6
Unemployed	4	5.9	0	0.0	4	3.7	0	0.0
Otherwise	3	4.4	5	7.5	6	5.6	2	7.1
Pain location (n = 153***)								
Head or face	16	9.5	21	12.8	31	11.8	6	8.5
Upper extremities	21	12.4	16	9.8	27	10.3	10	14.1
Neck or shoulders	38	22.5	39	23.8	59	22.5	18	25.4
Low back	47	27.8	45	27.4	75	28.6	17	23.9
Lower extremities	32	18.9	33	20.1	50	19.1	15	21.1
Otherwise	15	8.9	10	6.1	20	7.6	5	7.0
Number of pain sites (median, IQR)	2.0	1–4	2.0	1–4	2.0	1–4	3.0	1–3

SD: standard deviation; IQR: interquartile range; n: number of available participants/observations.
*Significant difference between care as usual and short form (p < 0.05).
**Significant difference between completers and drop-outs (p < 0.05).
***Pain sites: some patients reported several pain sites thus exceeding the number of participants.

Table 2. Treatment duration and differences in dosage between groups.

	Care as usual n = 81		Short form n = 72		p	95% CI
Received duration (weeks) (mean, SD)	11.7	(4.5)	10.8	3.9	0.323	−0.5 to 2.2
Received contact hours (mean, SD)	30.7	11.3	29.8	10.4	0.622	−2.7 to 4.4
Dropouts (n, %)	22	27%*	11	15%*		
Weeks (mean, SD)	6.0	3.7	5.1	2.2		
Shortened (n, %)	23	39%**	15	25%**		
Weeks (mean, SD)	−5.7	4.0	−3.4	2.6		
As planned (n, %)	22	37%**	20	33%**		
Extended (n, %)	14	24%**	26	42%**		
Weeks (mean, SD)	2.9	2.0	4.0	2.0		

SD: Standard deviation; CI: Confidence interval.
*% of total n = 153.
**valid % of completers n = 120.

research that may lead to major new insights. Because dosage has been a methodological blind spot in pain rehabilitation research, and dosage variables were defined and interpreted differently across studies, results of previous trials may have been biased by lack of control of dosage. If A is compared to B and A leads to superior results, it is expected that A is the treatment of choice. However, theoretically, if the dose of A was higher than B, the difference also might be explained by dosage of B [19]. Differences in dosage could also explain differences

between studies and could be a reason why some studies were not able to detect significant differences between interventions [18].

Weaknesses and strengths

A weakness of the study was that it had to be discontinued prematurely because too many programs in de short form group were extended. This caused lack of included patients and lack of

Table 3. Trial results based on intention to treat analysis of PDI scores and EQ5D scores between and within treatment groups.

	n	T0 Mean (SD)	n	T1 Mean (SD)	n*	Difference in means (SD)	95% CI	SMD
PDI total	144	37.0 (13.3)	119	25.8 (16.2)	112	9.6 (12.8)	7.2 to 12.0	0.8
Care as usual	74	36.1 (12.5)	63	25.1 (15.0)	58	10.8 (13.2)	7.3 to 14.3	0.8
Short form	70	37.9 (14.2)	56	26.6 (17.7)	54	8.3 (12.2)	5.0 to 11.6	0.7
ES between group difference						0.20		
EQ5D index total	125	0.55 (0.20)	101	0.70 (0.18)	93	0.13 (0.17)	0.09 to 0.17	0.8
Care as usual	66	0.56 (0.19)	54	0.70 (0.17)	51	0.11 (0.19)	0.06 to 0.17	0.6
Short form	59	0.54 (0.21)	47	0.70 (0.20)	42	0.15 (0.15)	0.10 to 0.19	1.0
ES between group difference						0.19		
EQ5D VAS	126	54.0 (17.7)	102	67.6 (17.3)	93	14.0 (18.8)	17.8 to 10.1	0.7
Care as usual	68	54.5 (17.8)	54	67.5 (16.1)	52	14.0 (20.7)	19.6 to 8.3	0.7
Short form	58	54.4 (17.7)	47	67.6 (18.7)	41	14.0 (17.0)	19.3 tot 8.6	0.8
ES between group difference						0		

T0: before program; T1: direct after program.
PDI: Pain Disability Index (scale 0–70); EQ5D: Euroqol 5D index (scale 0.0–1.0); VAS: visual analog scale (0–100).
SD: Standard deviation, CI: Confidence interval.
SMD: Standardised mean difference; ES: Effect Size.
n: number of available observations.
*Paired observations.

Table 4. Differences between subgroups of patients, who completed the trial, according to duration of pain rehabilitation program; shortened, as planned and extended.

	Shortened		As planned		Extended		
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	F value and p value
PDI T0	65	37.6 (14.0)	42	39.5 (11.0)	37	33.0 (14.0)	$F_{2,141} = 2.515, p = 0.085$
PDI T1	43	26.8 (15.9)	38	27.6 (16.6)	38	22.8 (16.2)	$F_{2,116} = 0.956, p = 0.387$
PDI T0–T1	39	8.1 (12.1)	38	11.4 (9.9)	35	9.4 (16.0)	$F_{2,109} = 0.640, p = 0.529$

PDI: Pain Disability Index (scale 0–70).
PDI T0: PDI score baseline, PDI T1: PDI score discharge.
PDI T0–T1: Differences between T0 and T1.
SD: Standard deviation; n: number of available observations.

Table 5. Differences between baseline characteristics and differences in PDI of patients according to duration of pain rehabilitation program; shortened, as planned and extended.

	Shortened n = 38			As planned n = 42			Extended n = 40				
	Mean	SD	(M)	Mean	SD	(M)	Mean	SD	(M)	Significance	
Age	45.3	14.1	(0)	41.1	12.2	(0)	42.8	11.3	(0)	$F_{2,117} = 0.972$	$p = 0.381$
Average pain last week	6.5	1.8		6.9	1.4		6.6	1.5	(4)	$F_{2,102} = 0.452$	$p = 0.638$
Worst pain last week	7.9	1.8		8.3	1.3		7.9	1.4	(2)	$F_{2,105} = 0.660$	$p = 0.519$
PDI T0–T1	35.5	13.5		39.5	11		33.0	14.0	(3)	$F_{2,111} = 2,569$	$p = 0.081$
	n	%		n	%		n	%			
Gender (% female)	28	73.7		29	69.0		22	55.0		$X^2 = 3.321$	$p = 0.190$
Duration of pain			(2)			(6)			(4)	$X^2 = 2.175$	$p = 0.337$
3 months to 1 year	4	12.1		3	8.3		1	2.8			
>1 year	29	87.9		33	91.7		35	97.2			

PDI T0–T1: Differences between T0 and T1; SD: Standard deviation.

contrast regarding dosage between the care as usual and short form groups, which may partly explain the inconclusiveness of the results. In addition, the small sample size caused a relative wide 95% CI, which also led to inconclusiveness. Different scenarios were considered and discussed with the team to shorten the program. Care as usual was offered in programmes of 8,12,16 and 20 weeks. In absence of evidence, it was decided to test shortening with one step (4 weeks). This could be considered a methodological weakness of the study because the relative impact differed between programmes (from 12 to 8 weeks: 33% reduction, 16 to 12 weeks: 25% reduction, 20 to 16 weeks: 20% reduction). On the other hand, adherence to care as usual strengthened this study because it reduced the risk of allocation bias in patients and rehabilitation team members.

Extension of treatment duration may be regarded as a limitation or even as an adverse event or programme violation. However, during this study, we were obliged to adhere to the Dutch health care regulations and the Medical Ethics Committee. As a consequence, we were not allowed to deny health care that was deemed necessary for good patient care. Within the field of pain rehabilitation there are no guidelines regarding dosage. As described in the introduction, pain rehabilitation programs aim to reduce disability and use of health care services. Patients are coached to self-manage pain and disability. As far as we know there are no published validated measures to assess these self-management skills. Consequently, it is unclear at what point a patient will be ready to self-manage his pain and disability, and when pain rehabilitation program is no longer of added value. Partly because of lack of evidence regarding dosage of pain rehabilitation program, choices of dosage are unclear and arbitrary. This may result in differences in dosage between and within pain rehabilitation programs. This is a weakness of this study because, in some cases this resulted in shortening or extending pain rehabilitation program in both the care as usual and short

form groups. On the other hand, this is an important reason for future research to focus on the rationale underlying dosage of pain rehabilitation program, including transparency of choices in dosage of treatment. This should eventually lead to more rational dosage of pain rehabilitation programs, including explicit arguments on which the choice of dosage for individual patients is based and result in development of validated measurements to determine program dosage.

A non-inferiority margin is chosen as the smallest value that would be a clinically important effect [20]. Based on the mean change of care as usual (10 points; near the 8.5–9.5 points of the MCIC) we a priori defined that a margin of 40% of 10 points of change (4 points), could be considered as similar. We acknowledge that this is an arbitrary margin, however, conducting the first study of this kind in our field, we could not build on guidelines, clinical evidence or consensus statements, which means that other margins would also be debatable. Only 76% of the randomized patients were included in the ITT analyses, which might have potentially introduced a bias in the results. We judge it as unlikely, because there is no indication of systematic differences between the groups.

A strength of this study is the pragmatic, clinical design; including the struggle of clinical practice regarding dosage of pain rehabilitation programs. This study shows results of shortening and extending pain rehabilitation programs. Based on the regression analyses, which showed that dosage did not significantly contribute to the model, extending does not directly lead to better results, nor does reducing pain rehabilitation program directly leads to worse results. As this was the first trial within pain rehabilitation to study dosage, we suggest replication in different settings, and that all future trials and observational studies in this field clearly describe dosage issues to enable future (meta-)analyses of trial results.

Because the CI of the mean difference exceeded the upper and lower limit of the non-inferiority margin, the results of this trial are inconclusive. In this study, a reduction of four weeks of pain rehabilitation program did not lead to non-inferior mean results.

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Disclosure statement

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References

[1] Airaksinen O, Brox JI, Cedraschi C, COST B13 Working Group on Guidelines for Chronic Low Back Pain, et al. Chapter 4. European guidelines for the management of chronic non-specific low back pain. Eur Spine J. 2006;15:S192–S300.

[2] Köke A, Brouwers M, Heuts P, et al. Consensus rapport pijnrevalidatie nederland. John Wiley & Sons, Ltd. 2005.

[3] Scascighini L, Toma V, Dober-Spielmann S, et al. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. Rheumatology (Oxford). 2008;47:670–678.

[4] Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. Cochrane Database Syst Rev. 2014;(9):CD000963.

[5] Waterschoot FP, Dijkstra PU, Hollak N, et al. Dose or content? effectiveness of pain rehabilitation programs for patients with chronic low back pain: a systematic review. Pain. 2014;155:179–189.

[6] Piaggio G, Elbourne DR, Altman DG, CONSORT Group, et al. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. Jama. 2006;295:1152–1160.

[7] Koke AJ, Smeets RJ, Schreurs KM, et al. Dutch dataset pain rehabilitation in daily practice: Content, patient characteristics and reference data. Eur J Pain. 2017;21:434–444.

[8] Tait RC, Chibnall JT, Krause S. The pain disability index: psychometric properties. Pain. 1990;40:171–182.

[9] Soer R, Koke AJ, Speijer BL, Groningen Spine Study Group, et al. Reference values of the pain disability index in patients with painful musculoskeletal and spinal disorders: a cross-national study. Spine (Phila Pa 1976). 2015;40:E545–E551.

[10] Gronblad M, Hupli M, Wennerstrand P, et al. Intercorrelation and test-retest reliability of the pain disability index (PDI) and the oswestry disability questionnaire (ODQ) and their correlation with pain intensity in low back pain patients. Clin J Pain.1993;9:189–195.

[11] Soer R, Reneman MF, Vroomen PC, et al. Responsiveness and minimal clinically important change of the pain disability index in patients with chronic back pain. Spine (Phila Pa 1976). 2012;37:711–715.

[12] Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727–1736.

[13] van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15:708–715.

[14] Soer R, Reneman MF, Speijer BL, et al. Clinimetric properties of the EuroQol-5D in patients with chronic low back pain. Spine J. 2012;12:1035–1039.

[15] Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: A multi-country study. Qual Life Res. 2013;22:1717–1727.

[16] Borestein M, Hedges LV, Higgens JPT, et al. Introduction to meta-analysis. Chichester (UK): Wiley; 2009.

[17] Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.

[18] Smeets RJ, Vlaeyen JW, Hidding A, et al. Active rehabilitation for chronic low back pain: Cognitive-behavioral, physical, or both? first direct post-treatment results from a randomized controlled trial [ISRCTN22714229. BMC Musculoskelet Disord. 2006;207:5.

[19] Bendix T, Bendix A, Labriola M, et al. Functional restoration versus outpatient physical training in chronic low back pain: a randomized comparative study. Spine (Phila Pa 1976). 2000;125:2494–2500.

[20] Piaggio G, Elbourne DR, Pocock SJ, CONSORT Group, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. Jama. 2012;308:2594–2604.