OVERVIEW OF THE PROJECT

Chronic low back pain is a massive health problem in Australia. The evidence is consistent that treatments for chronic back pain have only modest effects. Attempts to prevent chronic low back pain have focused on biomechanics, fear avoidance, work and social-related factors or activity. These approaches are not successful for many people.

We are taking an alternative approach and focusing on two factors that are fundamental determinants of pain, but have hitherto not been considered as potential targets for preventative intervention. The first factor is the *meaning* that an individual attaches to their pain as the meaning of noxious input ultimately determines whether or not it will be painful. Pain does not depend on the true danger to tissues, but on the brain's evaluation of that danger. The second factor is *mood*. Pain, unlike purely sensory perceptions has an affective component. It is this affect that gives pain such a strong survival value and mood cannot be separated from pain. There are very well-established biological pathways by which meaning and mood can upregulate the nociceptive system, leading to increased sensitivity of nociceptive and pain systems and, consequently, chronic pain.

Remarkably, very few attempts have been made to reduce the risk of chronicity by targeting the fundamental determinants of pain, meaning & mood, directly.

This project brings together international experts in several fields and represents the final stage of a decade of clinical and fundamental research. We have identified the factors associated with poor prognosis. We have thoroughly tested and refined a deceptively simple, easily implemented, and inexpensive intervention that targets these factors. We are able to identify the patients who are at high risk for developing chronic low back pain and for whom our novel treatment is ideally suited.

We are now ready to undertake the final stage of this work, the definitive prospective randomised placebo-controlled trial to evaluate if our intervention reduces the proportion of high-risk individuals who develop chronic back low pain.

1. PROJECT PRIMARY AIMS AND HYPOTHESIS

The aim of this project is to:

- Establish whether our novel psychoeducative intervention, *Explain Pain*, reduces the development of chronic low back in high-risk individuals.

We hypothesize that:

- The addition of *Explain Pain* to NHMRC guideline-based care for acute low back pain will reduce the proportion of patients who have persistent low back pain at 3 months.

2. BACKGROUND

The problem of chronic low back pain.

Low back pain is very common[1 2] but not everyone who gets low back pain will develop *chronic* low back pain. In fact, most do not[3]. In the largest ever study of its kind we showed that about 60% of people who have low back pain recover in a few weeks[4], often with minimal intervention[5]. However for the other 40% recovery is slow and the risk of persistent problems is very high (Figure 1). It is this 40% who incur most of the enormous costs associated with low back pain[6 7]. In Australia these patients represent a drain on the economy that is equivalent to building 120 new

general hospitals each year[8]. Any approach that reduces the incidence of chronic low back pain is likely to have a major national impact.

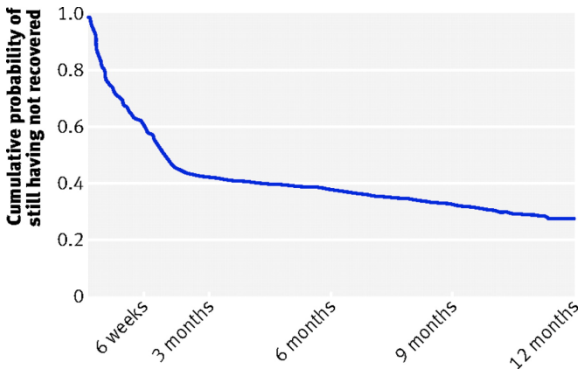

Figure 1: This graph shows that recovery is rapid in the first few weeks and months after an initial episode of low back pain and that it slows down markedly after 3 months, once chronic low back pain develops. (Henschke et al, 2008 BMJ[4]).

Our work, and that of others, has consistently shown that treatments for patients with chronic low back pain are seldom effective in returning them to a pain-free or productive life[9 10-12]. These people face a downward spiral of increasingly lengthy periods of severe pain and chronic disability with substantial social and personal disadvantage[2].

We are proposing that, rather than waiting to treat patients who already have chronic low back pain, much better outcomes are likely to be achieved if we intervene early to reduce the risk of developing chronic low back pain after an acute episode.

This proposal is both logical and aligned with the NHMRC's Preventative Health Care priority goal of the National Health Priority - Promoting and Maintaining Good Health.

<u>Biological plausibility of our approach: Changing the meaning of pain and mood of the patient will reduce chronicity</u>

Pain does not equate to tissue damage, nor does it equate to activity in nociceptors. We have known this for decades – Patrick Wall stated in 1986 that "the mislabelling of nociceptors as pain fibres was not an elegant simplification but an unfortunate trivialization"[13]. That multiple cognitive and contextual factors modulate pain is well established and the mantra that 'nociception is neither sufficient nor necessary for pain' is well accepted in the fundamental pain sciences[14 15]. It is also well established that the *meaning* of one's pain determines descending modulatory control of spinal nociceptors – the stronger one's pain is conceptualised as reflecting tissue damage, the more likely is descending facilitation of spinal nociceptors[16] – and sustained upregulation of spinal nociceptors is a key determinant of central sensitivity and chronic pain[17]. Thus, there is a direct neurological pathway by which the *meaning* of pain to the patient modulates the risk of chronic low back pain.

Evaluating a patient's *mood* is an important part of clinical triage[21] as is the notion that mood affects recovery. Recently, direct biological pathways by which *mood* can modulate chronicity have also been uncovered. Depression is associated with increased expression of pro-inflammatory cytokines, decreased expression of anti-inflammatory cytokines[18], and disruption of the HPA axis (see CIC Moseley – Explain Pain[15] & Blackburn-Munro (2007)[19]. All of these mechanisms upregulate spinal nociceptors and cortical networks implicated in chronic pain[20]. Thus, there is a direct neurological pathway by which *mood* modulates the risk of chronic low back pain.

Indirect pathways by which *meaning & mood* are likely to modulate the risk of chronicity are well recognised clinically – for example the strong belief that pain means damage, and the more one is depressed, the less likely one is to adopt behavioural strategies that promote recovery, for example

return to normal activity and engagement in social and work activities. While we endorse the validity of these indirect pathways, we contend that the direct pathways are more obvious and proximal targets of intervention.

THIS PROJECT AS THE CULMINATION OF A WIDER RESEARCH PROGRAMME

The four hallmarks of a successful preventative intervention are to (i) identify the factors that are associated with the development chronic low back pain (ii) develop interventions that treat these factors (iii) identify, at an early stage, patients who are at high-risk of developing chronic low back pain (iv) determine whether treating high-risk patients early with the novel intervention decreases the risk of chronicity. We have achieved the first three objectives. This proposal is to fund the final definite stage of our work.

(i) We have identified the factors that are associated with the development of chronic low back pain

Over the last decade, we have undertaken a series of major prognostic studies that have led to the identification of key variables associated with an increased risk of developing chronic low back pain after an acute episode[3 4 21 22]. Together these variables reflect the *meaning* of one's back pain to that individual and the *mood* of that individual. The major variables are: expectations of persistence, reductions in usual activities and symptoms of depression[4]. Patients at high-risk for chronicity have strong beliefs that they will not recover, that their pain is going to get worse (catastrophising) and that having pain means they should stop what they are doing until the pain goes away[23]. They also score highly on measures of depression. Recent systematic reviews that incorporate data from international cohorts have confirmed our findings[2 24]. International guidelines for the management of low back pain[25] and those working at the coalface, clinicians &injury managers[26], have reached similar conclusions - the influence of variables that reflect *meaning & mood* play a critical role on the development of chronic low back pain.

KEY POINT: Variables that reflect *meaning & mood*, are associated with the development of chronic low back pain.

(ii) We have developed a simple, easy to implement and inexpensive intervention to treat the factors associated with the development of chronic low back pain

The proposed project represents the final stage of over a decade of research into Explaining pain[15]. There is now a large amount of research that shows that carefully explaining to someone the biology that underpins pain changes the *meaning* of their pain. For example, explaining pain changes pain-related attitudes and beliefs, in particular it decreases the conviction that pain is an accurate indication of tissue damage and increases the conviction that pain is modulated by one's thoughts and beliefs. Explaining pain decreases pain-related catastrophising in people with chronic or subacute pain and in pain-free individuals[27-30]. A blinded randomized experiment showed that explaining pain increases pain threshold during a straight leg raise and explaining lumbar spine physiology and anatomy decreases pain threshold during a straight leg raise[31]. Explaining pain has also been shown to decrease pain and disability in people with chronic pain[32]. These findings have now been replicated in other languages and distinct chronic pain groups[29], and are supported by systematic reviews[33].

We have also completed a final pilot study. We predicted that by first shifting the meaning of pain via Explain Pain, the effects of a multidisciplinary programme that targets the indirect effects of meaning and mood on physical, social and work activity, would be enhanced. Chronic pain patients (n=104) were randomly allocated to Explain Pain or to best practice behavioural advice, based on

The Back Book[34], prior to participation in an intensive, cognitive-behavioural therapy based, pain management programme. Six months later, those who had undertaken Explain Pain before their programme, were doing better than those who had not: the odds ratio (OR) for a clinically meaningful reduction in pain was 3 (95% CI = 2 – 9). For disability, the OR was 9.5 (3 – 36). For a positive shift in work status, OR = 6 (2 – 22). That is, our hypothesis was soundly supported.

KEY POINT: Explaining pain modifies *meaning & mood*, leading to clinically relevant changes.

(iii) We can identify the patients who are at high risk of developing chronic low back pain
Treating all patients with acute low back pain to prevent them developing chronic low back pain is clearly inefficient as 60% will recover within a few weeks with minimal intervention[4]. Additional interventions are better targeted to those at high risk[35]. We aim to treat those patients who are at *high-risk* of developing chronic low back pain[36].

Our systematic review[37] of the Orebro Musculoskeletal Pain Screening Questionnaire (OMPSQ)[38] identified that it is suited for this purpose. A cut-off score of 120 on this questionnaire identifies 92% of those who will recover before three months and 75% who won't (Table 1). These patients were 4 times more likely to have chronic low back pain[39]. We have recently developed a short-form of this questionnaire which our testing indicates has similar properties to the long form[40].

Cut-off score	Recovered at 3 months (specificity %)	Not recovered at 3 months (sensitivity %)
105	82	46
110	84	43
120	92	25

Table 1 showing that scores on the OMPSQ under 120 are likely to identify almost all of the patients who recover and 75% of patients who don't recover (Linton and Boersma, 1997[38]).

Including patients with OMPSQ > 120 in our study will include only a few patients who are likely to recover early (<10%) and we will include almost 75% of those who are likely to develop chronic low back pain.

KEY POINT: The OMPSQ allow us to target moderate and high-risk patients and exclude nearly all who would normally go on to recover in a weeks with minimal intervention.

(iv) We have pilot tested our approach and found promising results.
The final step before we can definitely test our treatment is to undertake pilot work that demonstrates its feasibility in a clinical setting, and gives some projection of the likelihood that our hypothesis will be supported. We have now completed that step[41]. An initial consecutive cohort of 74 patients with occupational injuries participated and cost-of-injury data show that the OMPSQ successfully predicted poor outcomes. In a second consecutive cohort of 78 patients with occupational injuries, high-risk patients were treated early according to our conceptual model, and the costs of their management were reduced by 25%, principally via an earlier return-to-work. It is notable that savings were achieved despite the additional cost of intervention. This pilot study showed that we can identify patients at high risk of chronicity, intervene early and reduce the risk of chronicity.

Now it is time to fully interrogate our hypothesis using the gold-standard randomised placebo-controlled clinical trial.

3. RESEARCH PLAN, METHOD AND TECHNIQUES

Overview of the research design

The study will be a randomised controlled trial evaluating the effectiveness of a brief psychoeducative intervention to prevent the development of chronic low back pain in a group of acute low back pain patients who are at risk of developing chronic low back pain.

Patients with acute low back pain attending primary care (GP, physiotherapist or chiropractor) will be assessed for variables reflecting *meaning & mood*. Patients with high levels of these variables will be randomised to receive NHMRC guideline-based care *plus* sham psychoeducational intervention or guideline-based care *plus* an individualised psychoeducational intervention designed to address the *meaning & mood*. Outcomes will be assessed at 3, 6 and 12 months.

Patients

We will recruit primary care practitioners using our successful recruitment strategies[4 5 42]. The primary care practitioners will identify consecutive patients with low back pain and provide their contact details to the study researchers. The study researchers will apply the study inclusion/exclusion criteria and consent 250 acute low back pain patients to the study.

Inclusion criteria: Patients will be included if they meet all of the following criteria:

- The primary complaint of pain is in the area between the 12th rib and buttock crease. This may, or may not, be accompanied by leg pain.
- A new episode of low back pain, preceded by $\geq$ one month without low back pain[43].
- The duration of current symptoms is less than 4 weeks.
- An OMPSQ score greater than 120.
- Sufficient fluency in English language to understand and respond to English language questionnaires and to engage with the psychoeducative intervention.

Exclusion criteria: Patients will be excluded if they have any of the following conditions:

- Known or suspected serious spinal pathology, nerve root compromise, previous spinal surgery[44].
- Currently receiving care for a mental health condition.

Randomisation

A researcher not involved in patient recruitment or data collection will create a randomisation schedule using randomisation software. The schedule will be in randomly permuted blocks stratified for Work Cover/compensation claim. The schedule will be used to create 250 consecutively numbered, sealed, opaque envelopes containing allocations.

Procedure

During the consultation the primary care practitioner will contact the study researcher by telephone or email to provide the patient contact details. The study researcher will contact the patient by telephone within 24 hours of the first consultation to conduct the screening, consent and baseline assessments. Once the study researcher has obtained baseline data the patient will be randomised to receive NHMRC guideline care *plus* sham psychoeducative intervention or NHMRC guideline care *plus* the psychoeducative intervention.

All participants will be reminded to continue with the care provided by their primary care clinician for their low back pain. The study researcher will organise an initial appointment with the specially trained clinician to receive either the sham or active psychoeducative intervention.

NHMRC Guideline care

All patients will receive NHMRC guideline care. Participating general practitioners, physiotherapists and chiropractors will be trained in the delivery of guideline care based on the NHMRC guideline for recent onset low back pain[45]. The guideline recommends a first-line of care consisting of advice, reassurance and analgesics. Participants will be reassured of the benign nature of low back pain, advised to remain active and avoid bed rest, and instructed in the use of simple analgesics to manage their symptoms. The practitioner may consider second line options such as spinal manipulation if the patient does not respond to first-line care.

The psychoeducation program – *Explain Pain*

Patients randomised to the psychoeducative intervention will participate in 2 sessions of *Explain Pain* by the specially trained clinician. Our pilot study showed that 2 x 1-hour sessions is sufficient to change the meaning of pain and improve mood. All treatments associated with the intervention will be completed within 2 weeks of randomisation.

Explain Pain involves a collaborative clinician-patient interaction. The clinician determines key conceptual frameworks via a recognised questionnaire and targeted interview. The intervention has been refined on the basis of numerous clinical and experimental studies and is informed by current theory in health literacy, conceptual change and educational design. It follows this broad plan: (i) introduction of key concepts identified in assessment and interview, (ii) explanation of key concepts in biological terms, (iii) evaluation and embedding of key concepts. We have recently shown that metaphors and stories provide the best way to introduce key concepts[46]. Metaphors provide visualisation of abstract ideas and their abstraction from the targeted concept reduces cognitive resistance to the same. Thus, metaphors are thought to provoke contemplation and increase the potential for re-organisation of previous meanings.

The most common key concepts are: nociceptive input is modulated at the spinal cord and the brain; the brain evaluates many inputs before selecting a response; pain is the conscious part of the response; the brain modulates the nociceptive signal at the spinal cord. Emphasis is placed on the distinction between pain and nociception, on the biological necessity of multiple influences over pain, on the plasticity of the spinal cord and brain and the importance of neural changes in chronic pain. Explaining pain has strong theoretical support in conceptual change theory, which stipulates that conceptual change requires deep and superficial learning. Deep learning is information that is retained and understood and applied to problems at hand[47] and 'superficial' or 'surface' learning is information which is remembered but not understood or integrated with attitudes and beliefs[48]. Explaining pain takes about two hours. Two sessions will be devoted to explaining pain. Reconceptualisation will be evaluated using established questionnaires.

The sham psychoeducation intervention

Patients randomised to the sham psychoeducative intervention will receive 2 x 1 hour sessions of sham psychoeducative education, based on sham advice sessions reported in our previous study[49]. Patients will be given the opportunity to discuss their low back pain and any other problems that they may have. The clinician will respond in an empathetic way, but will not offer any advice or information on pain or their condition. We have previously shown patients find sham advice/education to be credible[49].

Sample size calculations.
We calculated sample size using the method of Twisk[50] for mixed models. With 2 repeated observations, an estimated intra-cluster correlation (correlation between the observations) of 0.4, alpha set at 5%, and allowing for 15% loss to follow up, we require 125 patients in each group to have an 80% power to detect a relative reduction in risk (i.e., in incidence proportion) of having low back pain at 3 months of 15%. This implies a number needed to treat (NNT) of 10. We consider these to be the smallest effects that would justify implementation of the intervention. In these calculations we have conservatively ignored the increase in statistical power conferred by baseline covariates and stratification.

Feasibility
We have been very successful in recruiting primary care practitioners for several similar trials[4 5 42 49]. We have developed strong links with local clinicians and have a network of practitioners who have expressed interest in participation in future trials. We have designed the trial to minimise the workload on practitioners and interference with normal clinical practice, which is in our experience essential in maintaining practitioners' involvement.

Our previous experience suggests that a primary care practitioner will refer approximately 2 acute low back pain patients for our trial each month. Our pilot study with injured workers suggests that 20% of these patients will be eligible for the trial. We will recruit 50 primary care practitioners who we anticipate will recruit on average 7 acute low back pain patients each over 18-24 months. This will be sufficient to reach our target of 250 patients. In a previous study[4] we recruited 1,600 acute low back pain patients from primary care practitioners over a 24-month period so we believe that our target recruitment of 250 patients can be easily achieved within 24 months.

Outcomes
a) The ***primary outcome*** will be the risk (incidence proportion) of having low back pain at 3 months. The 3-month follow up was chosen as the primary outcome as this is the most common definition of chronic low back pain[43 51] and reflects the time when a clear change in prognosis occurs (see figure 1[4])

Low back pain will be determined by numerical pain rating scale (NRS) score of pain intensity > 0, taken from the Chronic Pain Grade[52], a widely used composite measure of pain intensity and disability that provides a method for quantifying the severity of chronic symptoms.

b) The ***secondary outcomes*** will include a condition-specific measure of disability (Roland Morris Disability Questionnaire[53] (RMDQ), 0-24 scale), a patient-generated measure of function (Patient-Specific Functional Scale[54], 0-10 scale) and the OMPSQ[38] (to determine if *meaning & mood* have changed). Each will be assessed at 3, 6 and 12 months. We will also take a measure of recurrence at 12 months[55],

Data and treatment integrity
Trial data integrity will be monitored by regularly scrutinising data files for omissions and errors. All data will be double entered and the source of any inconsistencies will be explored and resolved. Treatment adherence will be determined by recording attendance at treatment sessions and by analysing participant activity diaries.

Statistical Analysis
The data will be analysed by intention-to-treat and by a statistician blinded to group allocation. We will analyse the effect of treatment separately for each outcome using linear mixed models with

random intercepts for individuals to account for correlation of repeated measures. The model will include terms for important prognostic factors measured prior to randomisation and specified a priori. As we stratified by workers compensation status in the allocation schedule the analysis will be stratified by this variable. We will obtain estimates of the effect of the intervention and 95% confidence intervals by constructing linear contrasts to compare the adjusted difference in proportions (dichotomous variables) or mean change (continuous variables) in outcome from baseline to each time point between the treatment and control groups.

Justification of study design

The sham-controlled trial includes key methodological features recognised as minimising bias (e.g. patient/clinician/outcome assessor blinding, concealed allocation, and intention to treat analysis). We will prospectively register the trial and publish the full trial protocol in an open-access journal. The trial report will conform to the extension of the CONSORT statement for non-pharmacological trials.

Evidence that project will be successfully completed on time

Our pilot work and a recent Australian study of patients acute low back pain suggests that 20% of patients will score OMSPQ > 120 and be appropriate for our study[56]. That means that we need to screen 1090 to recruit 250 patients to the study (table 1[38 39]). This is well within our capacity as we have screened recently recruited over 3000 patients with low back pain and recruited 1600 with acute low back pain in the same geographical area of Sydney that this study will be based. We have the relationships and systems in place in metropolitan Sydney to ensure recruitment and clinician engagement.

The team has a demonstrated track record of leading and managing large trials such as this to completion. The rigour of our work is reflected in where they have been published – *The Lancet*, *Annals of Internal Medicine, BMJ, Neurology* and *Pain*. Our team has the content expert in Explain Pain (CIC Moseley), a recognised world expert on psychological intervention for pain disorders (CI Nicholas).

OUTCOMES & SIGNIFICANCE

Given the cost of low back pain, both financial and personal, any reduction in the proportion of patients developing chronic low back pain is likely to be of major significance to Australian and international communities. This study will provide a definitive evaluation of the efficacy of an extremely promising new treatment designed to prevent chronic low back pain. If found to be favourable, these results will fundamentally change the way acute low back pain is managed in primary care.

1. Croft P, Blyth FM, van der Windt D. *Chronic Pain Epidemiology: From Aetiology to Public Health*. Oxford: Oxford University Press, 2003.
2. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. *The Lancet* 2012;379(9814):482-91.
3. Menezes Costa LCM, Maher CG, Hancock MJ, McAuley JH, Herbert RD, L.O.P. C. The prognosis of acute and persistent low back pain: a meta-analysis. *CMAJ* 2011;accepted for publication 27-Sep-2011.
4. Henschke N, Maher CG, Refshauge KM, Herbert RD, Cumming RG, Bleasel J, York J, Das A, McAuley JH. Prognosis in patients with recent onset low back pain in Australian primary care: inception cohort study. *BMJ* 2008;337:a171.
5. Hancock MJ, Maher CG, Latimer J, McLachlan AJ, Cooper CW, Day RO, Spindler MF, McAuley JH. Assessment of diclofenac or spinal manipulative therapy, or both, in addition to recommended first-line treatment for acute low back pain: a randomised controlled trial. *Lancet* 2007;370(9599):1638-43.
6. Krismer M, van Tulder M. Strategies for prevention and management of musculoskeletal conditions. Low back pain (non-specific). *Best Practice & Research Clinical Rheumatology* 2007;21:77-91.
7. Walker BF, Muller R, Grant WD. Low back pain in Australian adults: the economic burden. *Asia Pacific Journal of Public Health* 2003;15(2):79-87.
8. Rawlinsons_Group. *Rawlinson's Australian construction handbook*. Brisbane, Qld: Rawlhouse Publishing, 2006.
9. Machado LAC, Kamper SJ, Herbert RD, Maher CG, McAuley JH. Analgesic effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials. *Rheumatology* 2009;48(5):520-27.
10. Henschke N, Ostelo RWJG, van Tulder MW, Vlaeyen JWS, Morley S, Assendelft WJJ, Main CJ. Behavioural treatment for chronic low-back pain. *Cochrane Database of Systematic Reviews* 2010;Issue 7.
11. Costa LOP, Maher C, Latimer J, Hodges PW, Herbert RD, Refshauge KM, McAuley JH, Jennings MD. Motor control exercise for chronic low back pain: a randomized, placebo-controlled trial. *Physical Therapy* 2009;89(12):1275-86.
12. Macedo LG, Latimer J, Maher CG, Hodges PW, McAuley JH, Nicholas MK, Tonkin L, Stanton CJ, Stanton TR, Stafford R. Effect of Motor Control Exercises Versus Graded Activity in Patients With Chronic Nonspecific Low Back Pain: A Randomized Controlled Trial. *Physical Therapy* 2011.
13. Wall P, McMahon S. The relationship of perceived pain to afferent nerve impulses. *Trends Neurosci* 1986;9(6):254-55.
14. Price DD. *Psychological Mechanisms of pain and analgesia*. Seattle: IASP Press, 2000.
15. Butler D, Moseley GL. *Explain pain*. Adelaide: NOI Group Publishing, 2003.
16. Price DD. Neuroscience - Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000;288(5472):1769-72.
17. Woolf CJ, Salter M. Plasticity and pain: the role of the dorsal horn. In: McMahon SB, Koltzenburg M, editors. *Wall and Melzack's Textbook of Pain*, 2005.
18. Connor TJ, Leonard BE. Depression, stress and immunological activation: The role of cytokines in depressive disorders. *Life Sci* 1998;62(7):583-606.
19. Blackburn-Munro G. Hypothalamo-pituitary-adrenal axis dysfunction as a contributory factor to chronic pain and depression. *Current Pain and Headache Reports* 2007;8(2):116-24.
20. Ren K, Dubner R. Interactions between the immune and nervous systems in pain. *Nat Med* 2010;16(11):1267-76.

21. Costa LCM, Maher CG, McAuley JH, Hancock MJ, Herbert RD, Refshauge KM, Henschke N. Prognosis for patients with chronic low back pain: inception cohort study. *BMJ: British Medical Journal* 2009;339.
22. Hancock MJ, Maher CG, Latimer J, Herbert RD, McAuley JH. Can rate of recovery be predicted in patients with acute low back pain? Development of a clinical prediction rule. *European Journal of Pain* 2009;13(1):51-55.
23. Main CJ, Foster N, Buchbinder R. How important are back pain beliefs and expectations for satisfactory recovery from back pain? *Best Practice & Research Clinical Rheumatology* 2010;24:205-17.
24. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? *JAMA* 2010;303(13):1295-302.
25. Koes BW, van Tulder M, Lin CWC, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *European Spine Journal* 2010;19(12):2075-94.
26. WorkCover_SA. A guide to assessing and managing red and yellow flags for workers compensation patients, 2007.
27. Moseley GL, Nicholas MK, Hodges PW. A randomized controlled trial of intensive neurophysiology education in chronic low back pain. *Clin J Pain* 2004;20(5):324-30.
28. Moseley L. Unraveling the barriers to reconceptualization of the problem in chronic pain: the actual and perceived ability of patients and health professionals to understand the neurophysiology. *The Journal of Pain* 2003;4(4):184-89.
29. Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen S. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Arch Phys Med Rehabil* 2010;91(8):1153-59.
30. Ryan CG, Gray HG, Newton M, Granat MH. Pain biology education and exercise classes compared to pain biology education alone for individuals with chronic low back pain: a pilot randomised controlled trial. *Man Ther* 2010;15(4):382-87.
31. Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. *Eur J Pain* 2004;8(1):39-45.
32. Louw A, Diener I, Butler DS, Puentedura EJ. The Effect of Neuroscience Education on Pain, Disability, Anxiety, and Stress in Chronic Musculoskeletal Pain. *Arch Phys Med Rehabil* 2011;92(12):2041-56.
33. Clarke CL, Ryan CG, D.J. M. Pain neurophysiology education for the management of individuals with chronic low back pain: systematic review and meta-analysis. *Man Ther* 2011;16(6):544-9.
34. Roland M, Waddell G, Klaber-Moffet J, Burton K, Main CJ, Cantrell T. *The Back Book*. Norwich, UK: The Stationery Office, 1997.
35. Sattelmayer M, Lorenz T, Roder C, Hilfiker R. Predictive value of the Acute Low Back Pain Screening Questionnaire and the Orebro Musculoskeletal Pain Screening Questionnaire for persisting problems. *Eur Spine J* 2011;Accepted: 2 July 2011.
36. Nicholas MK, Linton SJ, Watson PJ, Main CJ. Early Identification and Management of Psychological Risk Factors ("Yellow Flags") in Patients With Low Back Pain: A Reappraisal. *Physical Therapy* 2011;91(5):737-53.
37. Hockings RL, McAuley JH, Maher CG. A systematic review of the predictive ability of the Orebro Musculoskeletal Pain Questionnaire. *Spine* 2008;33(15):E494.
38. Linton SJ, Halldén K. Can we screen for problematic back pain? A screening questionnaire for predicting outcome in acute and subacute back pain. *Clinical Journal of Pain* 1997;14:209-15.

39. Grotle M, Vøllestad NK, Brox JI. Screening for yellow flags in first-time acute low back pain: reliability and validity of a Norwegian version of the Acute Low Back Pain Screening Questionnaire. *Clinical Journal of Pain* 2006;22:458-67.
40. Linton SJ, Nicholas MK, MacDonald S. Development of a Short Form of the Örebro Musculoskeletal Pain Screening Questionnaire. *Spine* 2011;36(22):1891–95.
41. Pearce G, McGarity A, Nicholas MK, Linton SL, Peat JK. Better outcomes in worker's compensation through very early selective intervention. *Australasian Fac of Occup & Enviro Med & Australasian Fac of Rehab Med Combined Sci Meeting*
Volume: Adelaide, Australia 2008.
42. Machado LAC, Maher CG, Herbert RD, Clare H, McAuley JH. The effectiveness of the McKenzie method in addition to first-line care for acute low back pain: a randomized controlled trial. *BMC Medicine* 2010;8(10):Epub.
43. de Vet H, Heymans M, Dunn KM, Pope D, van der Beek A, Macfarlane GJ, Bouter LM, Croft PR. Episodes of Low Back Pain. A Proposal for Uniform Definitions to Be Used in Research. *Spine* 2002;27:2409-16.
44. Henschke N, Maher CG, Refshauge KM, Herbert RD, Cumming RG, Bleasel J, York J, Das A, McAuley JH. Prevalence of and screening for serious spinal pathology in patients presenting to primary care with acute low back pain. *Arthritis and Rheumatism* 2009;60(10):3072-80.
45. NHMRC. Evidence-Based Management of Acute Musculoskeletal Pain. Canberra, 2003.
46. von Bertouch L, McAuley JH, Moseley GL. A randomised controlled trial of using a book of metaphors to reconceptualise pain and decrease catastrophising in people with chronic pain. submitted.
47. Sandberg J, Barnard Y. Deep learning is difficult. *Instruc Sci* 1997;25:15-36.
48. Evans B, Honour L. Getting inside knowledge: The application of Entwistle's model of surface/deep processing producing open learning materials. *Educ Psychol* 1997;17:127-39.
49. Pengel LHM, Refshauge KM, Maher CG, Nicholas MK, Herbert RD, McNair P. Physiotherapist-directed exercise, advice, or both for subacute low back pain: a randomized trial. *Annals of Internal Medicine* 2007;146(11):787-96.
50. Twisk JWR. Sample size calculations. *Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide*. Cambridge: Cambridge University Press, 2003:280-85.
51. Von Korff M, Saunders K. The course of back pain in primary care. *Spine* 1996;21(24):2833-7.
52. Von Korff M, Ormel J, Keefe FJ, F. DS. Grading the severity of chronic pain. *Pain* 1992;50(2):133-49.
53. Roland M, Morris R. A study of the natural history of back pain. *Spine* 1983;8(2):141-50.
54. Stratford P, Gill C, Westaway M, Binkley J. Assessing disability and change on individual patients: a report of a patient specific measure. *Physiotherapy Canada* 1995;47(4):258-63.
55. Stanton TR, Latimer J, Maher CG, Hancock MJ. How do we define the condition 'recurrent low back pain'? A systematic review. *European Spine Journal* 2010;19(4):533-39.
56. Gabel CP, Melloh M, Yelland M, B. B, Roiko A. Predictive ability of a modified O¨rebro Musculoskeletal Pain Questionnaire in an acute/subacute low back pain working population. *Eur Spine J* 2011;20:449-57.

Summary of changes from original to published study protocol

- Added Markus Huebscher, Adrian Traeger, Hopin Lee, and Ian Skinner to list of investigators
- Include referring practitioner's rooms as study treatment locations
- Add inclusion criterion of pain intensity ≥3/10 on numeric rating scale (NRS) during the past week
- Use locally developed and validated prognostic model (PICKUP), instead of Orebro Musculoskeletal Pain Questionnaire, with score of >2.3 cutoff for inclusion (equivalent to >30% absolute risk of developing chronic low back pain)
- Add exclusion criterion of chronic spinal pain
- Specify that both study intervention sessions must occur within 2 weeks of initial presentation
- Primary outcome changed from dichotomous pain intensity scale (>=2/10 NRS, y/n) at 3 months to continuous pain intensity scale (0-10) at 3 months; sample size revised down from n=250 to n=202.
- Added all secondary outcomes & process measures listed in published protocol except for Roland Morris Disability Questionnaire.

Summary of changes from original to published statistical/mediation analysis plans

- Sample size calculation revised from detecting a relative risk reduction of having >=2/10 pain intensity scale at 3 months, to detecting a 1-point difference on a continuous pain intensity scale at 3 months.
- Prognostic factors not to be included in primary analysis
- Randomisation not to be stratified by worker's compensation status (because this factor was part of the risk screening algorithm which determined inclusion)
- Inclusion of a mechanism analysis (mediation analysis – see file number 6 in this Supplement for full protocol)