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Describing the Characteristics, Treatment Pathways and Outcomes of People with Chronic Low Back Pain Managed by a Pain Management Service in Nottingham and Generating Indicative Estimates of Cost-Effectiveness

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Abstract

Background: Chronic low back pain (CLBP) is a highly prevalent condition that has substantial impact on patients, the healthcare system and society. Its aetiology is complex and the condition can be exacerbated by many psychological, physical and social factors. Pain management services (PMS), which aim to address the complex nature of back pain, are recommended in clinical practice guidelines to manage CLBP. Although the effectiveness of such services has been widely investigated in relation to CLBP, the quality of evidence underpinning the use of these services remains moderate. Given that these services are resource intensive, evidence is needed to determine their cost-effectiveness.

Aim: This study aims to describe the patient characteristics, clinical outcomes and healthcare resource use of people with CLBP in a community-based pain management service (PMS) in Nottingham to derive an indicative estimate of the cost effectiveness of PMS compared with standard care (SC).

Methods: The study followed the Medical Research Council (MRC) guidance for evaluating complex interventions. The MRC suggest conducting developmental and observational work before evaluating complex interventions on a larger scale. Therefore, this PhD research includes a service evaluation study, which was conducted in two community-based PMS in Nottingham. This was followed by a systematic review of the cost effectiveness of a PMS in CLBP. Finally, a decision analysis model was developed to assess the cost effectiveness of PMS compared with SC.

In the service evaluation study, newly referred people with CLBP who provided written consent were included. Participants provided information on health status and healthcare resource use using postal questionnaires and diaries at baseline and then three and six months after recruitment. The outcome measures were the Brief Pain Inventory (BPI), the Roland Morris Disability Questionnaire (RMDQ) and the EuroQoL (EQ-5D-3L).

In the systematic review, electronic searches were conducted in clinical and economic databases from their inception to August 2017. Full economic evaluations, undertaken from any perspective, conducted alongside randomised clinical trials (RCTs) or based on decision analysis models were included. The Cochrane Back Review Group (CBRG) risk assessment and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist were used to assess the methodological quality of eligible studies. These studies informed the development of an economic evaluation based on a decision analysis model to compare PMS with SC. Costs per extra quality-adjusted-life-year (QALY) were calculated from the UK National Health Service (NHS) England perspective using a lifetime horizon. Transition probability, utilities, healthcare resource use and costs were obtained from the service evaluation study and the published literature.

Results: In the service evaluation study, 32 people were recruited over 10 months. The mean age was 58.8 years with an equal distribution of both genders. The dropout rates were 21% and 25% over three and six months respectively.

Disability was measured using RMDQ (with a score range between 0-24), where higher scores mean more disability. The mean score at baseline was 13.5, after three and six months the means were 11.9 and 11.1 respectively. The BPI was used to measure pain intensity and interference. The scores ranged from 0 to 10, where higher scores mean more pain. The mean score for pain intensity was 5.9 at baseline, followed by a mean of 5.5 and 5.6 at three and six months respectively, whereas pain interference was 5.9 at baseline, followed by a mean of 5.2 at three and six months. As for the EQ5D-3L, higher scores in EQ5D means better health states. The mean score was 0.38 at baseline and, after three and six months, the scores were 0.46 and 0.40 respectively. The mean number of health visits per patient between baseline and three months was 4, whereas between four and six months the mean number of visits per patient was 2.9.

In the systematic review, five studies fulfilled the eligibility criteria. The PMS varied significantly between studies in terms of the number of treatment modalities, intensity and the duration. The PMS was compared with either standard care, which varied according to the country and the setting or with two different surgical interventions. In this review, three out of five studies had a high risk of bias based on the design of the randomised controlled trials (RCTs). In addition, there were limitations in the statistical and sensitivity analyses in the economic evaluations. Therefore, the results from this systematic review need to be interpreted with caution. Finally, the indicative economic evaluation showed thatthe PMS was both more effective and more costly compared with SC. The mean incremental cost effectiveness ratio (ICER) was £761.43 and £706.98 per quality adjusted life years (QALY) gained in the deterministic and probabilistic analyses, respectively. At a ceiling willingness to pay (WTP) of £20,000,

the PMS reaches a 51% probability of being cost-effective. This suggest that there is 51% probability that the PMS is both more effective and less costly. The incremental net monetary benefit generated a mean of £7884.07, indicating that the PMS is cost-effective compared with the SC at a WTP of £20,000.

In the sensitivity analysis, the results were affected by changing the utility score for severe pain and increasing the initial cost of the intervention. In the scenario analysis, the incremental cost and QALYs were in favour of the PMS for people with severe pain at baseline. The probability of the PMS being cost effective for people with severe pain was 54%. In addition, the sustained reduction in treatment effect reduces the PMS probability of being cost effective to 48%. Finally, using the two months' data to generate the transition probabilities demonstrated that PMS dominates the SC and the probability of the PMS being cost effective was 58%

Conclusion: Community-based PMS have the potential to improve functional disability and pain interference for people with CLBP in primary care by providing well-timed access to a specialised pain management team, ensuring effective use of pain medicines and streamlining the treatment pathways based on the individual patient's needs.

A systematic literature review highlighted inconsistent evidence supporting PMS. The cost effectiveness studies included in this systematic review were alongside RCTs with a maximum follow up period of two years. As a result of the limitations of this type of economic evaluation, a decision analysis model was developed in order to assess the life time effectiveness of PMS compared with SC.

The decision analysis model showed that PMS is more effective and costly compared with SC in the base case analysis; however, changing the source of transition probabilities from 12 months to two months demonstrated that PMS dominated SC, providing the potential for PMS to be cost-effective if high quality research is conducted to reduce the uncertainty around transition probabilities. The results were also sensitive to change in the utility score for severe pain, the initial cost of the PMS and using the PMS for people with severe pain at baseline. Therefore, further information is needed to assess the uncertainties in these parameters to provide a more robust estimate of the cost-effectiveness of PMS compared with SC.

Dedication

This thesis is dedicated to

My parents,

My sisters and brother,

My nieces.

Acknowledgement

I give thanks to Allah for allowing me the opportunity, the strength and the patience to finally complete my thesis, after all the challenges and difficulties that I have faced. This thesis was the result of the collective efforts of a number of important and valued people who, directly or indirectly, assisted and supported me during my doctoral studies. To these people, I owe my gratitude and thanks. I would like to express my sincere gratitude to my supervisors, Rachel Elliott and Roger Knaggs, for their regular follow-up, continuous support and guidance in developing and executing this research. I would also like to thank Dr. Von Korff for providing me with his patients-level data to enable me to derive the inputs for my economic evaluation. I would also like to thank Dr. Hobbs, Dr. Lim and Heidi Lewis for facilitating the process of the study. I give special thanks to Antony Chuter for reviewing all patient-related paperwork, which include questionnaires, diaries, patient information sheets, and the consent form. Moreover, I would like to thank Lukasz Tanajewski and Georgios Gkountouras, who helped me in developing and validating my model inputs. I also would like to express my warmest and deepest appreciation to my best friend and colleague, Shiekha AlAujan, for her assistance, continuous support and understanding throughout this PhD journey.

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List of publications

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AlAujan, S., S. **AlMazrou,** R. D. Knaggs and R. A. Elliott (2016). "Describing the characteristics, treatment pathways, outcomes, and costs of people with persistent non-cancer pain managed by community pain clinics and generating an indicative estimate of cost-effectiveness: feasibility study protocol." Journal of Multidisciplinary Healthcare. 9: 237-245.

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Table of Contents

Abstract 2
Dedication 7
Acknowledgement 8
List of publications 9
Table of Contents 10
List of Figures 15
List of Tables 16
List of Abbreviations 18
Chapter 1 Introduction 19
1.1 Introduction 20
1.2 Structure of the Thesis 24
Chapter 2 Literature Review, Aim and Objectives 27
2.1 Introduction 28
2.2 The Definition of Back Pain 28
2.3 Natural History and the Clinical Course of Back Pain 29
2.4 The Epidemiology of Back Pain 30
2.5 The Personal and Economic Burden of Back Pain 31
2.6 The Assessment and Management of CLBP 34
2.6.1 Treatment Overview 38
2.6.2 Chronic Low Back Pain Guidelines 40
2.6.3 Cost effectiveness of CLBP treatments 43
2.7 The Biopsychosocial Model and Pain Management Services 46
2.8 Pain Management Service Terminology 47
2.9 Effectiveness and Cost Effectiveness of PMS in CLBP 48
2.10 Pain Management Services in the UK 51
2.11 Literature Review Summary 52
2.12 PMS in Nottingham 53
2.13 Study Justification 55
2.14 Methodology Justification 57
2.15 Aim and Objectives 58
Chapter 3 Describing the Characteristics, Treatment Pathways, Outcomes and Healthcare Resource use of People with Chronic Low Back Pain Managed by the Pain Management Service in Nottingham: A Service Evaluation Study 59

3.1 Introduction 60
3.2 Method 61
3.2.1 Study Design and Setting 61
3.2.2 Sample Size and Justification 61
3.2.3 Inclusion Criteria 61
3.2.4 Exclusion Criteria 62
3.2.5 Health Status Measures 62
3.2.5.1 Reason for Selecting these Health Status Measures 65
3.2.6 Recruitment 67
3.2.7 Ethical Considerations 69
3.2.7.1 Ethical Approval 69
3.2.7.2 Ethical Amendment 69
3.2.7.3 Process of Obtaining Consent 70
3.2.7.4 Participant Payment 70
3.2.7.5 Study Period Extension 70
3.2.7.6 Informed Consent 70
3.2.8 Data Security and Participant Confidentiality 71
3.2.9 Data Management 71
3.2.10 Statistical Analysis 72
3.3 Results 73
3.3.1 Recruitment Process: Challenges and Changes 73
3.3.2 Comparison between Respondents and Non-respondents 77
3.3.3 Baseline Characteristics 78
3.3.4 Comorbidities 80
3.3.5 Health Status Measures 81
3.3.5.1 Achieving minimal clinically important difference (MCID) in health status measures 84
3.3.6 Medicines Use 87
3.3.7 Healthcare Resource Use 94
3.4 Discussion 95
3.4.1 Feasibility of Recruitment and Retention 95
3.4.2 Feasibility of Data Collection Tools 98
3.4.3 Potential Clinical Effectiveness 99
3.4.4 Strengths and Limitations 102
3.5 Conclusion 103

Chapter 4 Cost-Effectiveness of Pain Management Services (PMS) for Chronic Low Back Pain: A Systematic Review of Published Studies 104
4.1 Introduction 105
4.2 Methods 106
4.2.1 Types of studies 106
4.2.2 Types of participants 106
4.2.3 Types of interventions 107
4.2.4 Types of outcome measures 107
4.2.5 Search methods for study identification 108
4.2.6 Methodological quality assessment 108
4.3 Results 109
4.3.1 Study characteristics 111
4.3.2 Methodological design 114
4.3.3 Design and description of pain management services 119
4.3.4 The comparator 121
4.3.5 Healthcare resource use and cost 121
4.3.6 Statistical analysis 124
4.3.7 Dealing with uncertainty 125
4.3.8 Cost-effectiveness of PMS 126
4.3.9 Economic evaluation using decision analysis models 128
4.4 Discussion 129
4.5 Conclusion 133
Chapter 5 Constructing a Markov Model to Evaluate the Cost Effectiveness of a Pain Management Service Compared with Standard Care for Adults with Chronic Low Back Pain 134
5.1 Introduction 135
5.2 Objectives 135
5.3 Methods 136
5.3.1 Intervention and Comparator 136
5.3.2 Pain Management Service Pathway 137
5.3.3 Standard care pathway 139
5.3.4 Study population 141
5.3.5 Structure of the Economic Model 141
5.3.6 Data Sources for Model Inputs 145
5.3.6.1 Transition Probabilities 147

5.3.6.2 Using Life Tables to Estimate All-Cause Mortality 151
5.3.6.3 CLBP and Increased Risk of Mortality 151
5.3.6.4 Utilities, Healthcare Resource Use and Costs 155
5.3.6.5 Assumptions about attrition of effect size 159
5.3.6.6 Subgroup Analysis 160
5.3.7 Cost Effectiveness Analysis 161
5.3.8 Model Validation 164
5.4 Results 165
5.4.1 Base case Analysis 165
5.4.2 One-way Sensitivity Analyses 168
5.4.3 Scenario Analyses 171
5.4.3.1 Subgroup by Pain Intensity Level 171
5.4.3.2 Assessing Change in the Treatment Effect over Time 172
5.4.3.3 Using two months' data to derive three months' probabilities 173
5.5 Discussion 174
5.6 Conclusions 178
Chapter 6 Discussion and Conclusion 179
6.1 Introduction 180
6.2 Summary of Key Research Findings 180
6.3 Strengths and weaknesses 182
6.4 Thesis contribution 184
6.5 Recommendations 185
6.6 Recommendations arising from the Service Evaluation Study 185
6.6.1 Recruitment and Retention 185
6.6.2 Selecting a Comparator Group 186
6.6.3 Healthcare Resource Use Data Collection 187
6.6.4 Patient and Public Involvement 188
6.7 Recommendations arising from the Systematic Review 188
6.8 Recommendations arising from Economic Evaluation 189
6.8.1 The Limitation in the Quality of Evidence Used to Inform the Model 189
6.8.2 Patient Characteristics and Intervention Intensity 190
6.8.3 Initial Cost of the PMS 192
6.8.4 Long-term Effectiveness 192
6.9 Implication for Practice and Patients 193
6.10 Implications for Policy Makers 193

6.11 Implications for Research 194
6.12 Conclusion 197
References 199
Appendices 238
Appendix A: Baseline questionnaire 239
Appendix B: Ethical approval 250
Appendix C: Ethical amendments 251
Appendix D: Consent form 252
Appendix E: Patient information sheet 253
Appendix F: Search strategy 257
Appendix G: CHEERS items 258
Appendix H: List of excluded studies and reasons for exclusion 263
Appendix I: National life tables (2013-2015) 264
Appendix J: CLBP related resource use per patient, by pain level, for participants providing data at six months from the IMPaCT Back trial [a] 265
Appendix K: Health services unit cost included in the model 266

List of Figures

Figure 2-1 Description of the PMS in Nottingham 54
Figure 3-1 Recruitment flow 74
Figure 3-2 Stratification of people based on MCID in functional disability using RMDS over the follow up period (n=32) 85
Figure 3-3 Stratification of people based on pain intensity score over the follow up period (n=32) 86
Figure 3-4 Stratification of people based on pain interference score over the follow up period (n=32) 87
Figure 4-1 Flow Chart Diagram 110
Figure 5-1 PMS pathway 138
Figure 5-2 SC pathway 140
Figure 5-3 Decision analysis model for PMS economic evaluation 144
Figure 5-4 Cost-effectiveness plane of probabilistic incremental costs and incremental QALY gain of the PMS versus SC 167
Figure 5-5 Cost effectiveness acceptability curve of PMS versus SC 167
Figure 5-6 Tornado diagram of one-way sensitivity analyses reporting changes in incremental cost effectiveness ratio (ICER) 170

List of Tables

Table 2-1 Psychometric properties for the commonly used health status measures in CLBP (84) 37
Table 2-2 Effectiveness of Pharmacologic and Nonpharmacologic Treatments for chronic low back pain 39
Table 3-1 Number of participants approached and responses received during the 10 month recruitment period 76
Table 3-2 Comparison between responders and non-responders 77
Table 3-3 Baseline characteristics of study participants 79
Table 3-4 Type of comorbidity among study participants 80
Table 3-5 Summary of health status measures over follow up period 82
Table 3-6 The mean difference between baseline, three and six month data 83
Table 3-7 Common medicines used by study participants 88
Table 3-8 Mean medicines use per patient stratified by medicines class over the follow up period 90
Table 3-9 Mean medicines use per patient stratified by medicines item over the follow up period 91
Table 3-10 Use of medicines combination over the follow up period 93
Table 3-11 Mean healthcare resource use per patient stratified by type of visits over the follow up 94
Table 3-12 Disaggregated mean healthcare resource use per patient stratified by type of visits over the follow up 95
Table 4-1 Characteristics of the included studies 112
Table 4-2 Risk of bias assessment according to the Cochrane Back Review Group (CBRG) 115
Table 4-3 Assessment of economic evaluations based on CHEERS criteria (inputs to economic evaluation: costs and outcomes) 117
Table 4-4 Economic evaluation based on CHEERS criteria (statistical analysis and results) 118
Table 4-5 Service description in the included studies 120
Table 4-6 Summary of incremental cost effectiveness analysis results 127
Table 5-1 Initial distribution for people with CLBP 141
Table 5-2 Transition probabilities and the number of people in each health state at twelve months 150

Table 5-3 Transition probabilities in each health state at three months 151
Table 5-4 Revised transition probability matrix for intervention arm and standard care where transitions to dead state vary with the age of the patients. 154
Table 5-5 Utilities derived from the IMPaCT Back study (202) 155
Table 5-6 Mean CLBP related healthcare resource use (HCRU) per patient and unit costs, by pain intensity level at three months 158
Table 5-7 Mean CLBP related costs per patient, by pain intensity level at three months ... 159
Table 5-8 One-way sensitivity analysis of the pain management service versus standard care 169
Table 5-9 ICERs, percentage ICERs in each quadrant and probability of cost effectiveness at $\lambda <$ £20,000 for base case, scenario analyses by pain intensity level at baseline 171
Table 5-10 ICERs, percentage ICERs in each quadrant and probability of cost effectiveness at $\lambda <$ £20,000 for base case, scenario analyses by changing the treatment effect over time 172
Table 5-11 ICERs, percentage ICERs in each quadrant and probability of cost effectiveness at $\lambda <$ £20,000 for base case, scenario analyses by using two months' data to derive probabilities 173

List of Abbreviations

AdViSHE	The Assessment of the Validation Status of Health-Economic decision models
BPI	Brief Pain Inventory
CBRG	Cochrane Back Review Group
CBT	Cognitive behavioural therapy
CCG	Clinical commissioning group
CEAC	Cost effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CLBP	Chronic low back pain
CMO	Chief Medical Officer
EQ5D	EuroQol 5 dimensions
GP	General practitioner/practice
HTA	Health technology assessment
IASP	International Association for the Study of Pain
ICER	Incremental cost effectiveness ratio
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
INMB	Incremental net monetary benefit
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MRC	Medical research council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAIDs	Non-steroidal anti-inflammatory drugs
ODI	Oswestry Disability Index
PMS	Pain management service
QALY	Quality adjusted life years
RCT	Randomised controlled trials
RMDQ	Roland Morris Disability Questionnaire
SC	Standard care
SMD	Standardised Mean Difference

Chapter 1

Introduction

1.1 Introduction

This PhD research focuses on the effect of a community-based pain management service (PMS) on people with chronic low back pain (CLBP) . Other types of back pain, including acute, subacute or back pain associated with other conditions, such as cancer or infections, are beyond the scope of this research.

The research involved a number of interrelated but, nonetheless, discrete studies, each building consecutively on the other to generate an indicative estimate of cost effectiveness.

Non-specific CLBP is tension, soreness and/or stiffness between the lowest ribs and the inferior gluteal folds for which it is difficult to identify a specific cause of the pain, with this pain lasting for more than three months (1).

CLBP is highly prevalent worldwide, affecting 19.6 % of the general population (2). CLBP has substantial effects on physical function, psychological wellbeing and quality of life (3-5). According to the Global Burden of Disease Study in 2010 (6), CLBP was the 3rd leading cause of disability adjusted life years (DALYs) after ischaemic heart disease and chronic obstructive pulmonary disease (COPD). The economic burden of CLBP is also substantial. People with CLBP are significant utilisers of healthcare resources (7). Furthermore, indirect costs to society are significant, partially due to lower productivity and higher absenteeism (8).

Managing non-specifc CLBP is challenging due to many factors. Firstly, the aetiology and clinical course is complex (9). People with CLBP who seek treatment in primary

care show large variations with regard to recovery or improvements during the first months. The evidence has found that people with CLBP achieve a rapid recovery in symptoms, which lasts for six months after treatment initiation, followed by a plateau. This trend of change is achieved regardless of the treatment provided (10, 11).

In addition, it can be exacerbated by a wide range of socio-demographic, physical and psychosocial factors, such as illness behaviour beliefs and distress (9, 12). Therefore, no single treatment is adequate to control all symptoms in all patients.

In order to manage CLBP within a biopsychosocial framework, which addresses pain as a dynamic interaction between physiological, social and psychological elements, pain management services (PMS) based on cognitive behavourial approaches are recommended by national and international guidelines (13, 14). The effectiveness of such services has been widely investigated in relation to back pain. However, the quality of evidence underpinning the use of these services remains moderate (15).

Given that this management approach is resource intensive (16, 17), evidence is needed to demonstrate the cost effectiveness of such intervention. A small number of cost effectiveness studies have been undertaken in Europe and the United States of America (USA) (18-22) and others are in progress in Spain and the Netherlands (23, 24). These studies were conducted alongside RCTs; however, they have methodological limitations in study design. Compliance to treatment was either inadequate (20, 21, 25) or not clearly reported (22, 26). Moreover, some aspects of the treatments/sessions did not appear to be equally used by all participants (21, 25). Therefore, the effect cannot be directly attributed to the pain management service.

In addition, threats to external validity might impede the application of the results to real practice. These threats come from restrictive patient eligibility criteria, such as employees (20, 26), recruiting from various practice settings, ie, primary and secondary care settings, and the intervention variability. This variability is either between intervention in terms of treatment components and healthcare staff or between study participants. Therefore, the results relating to the cost effectiveness of these services have been inconclusive due to the variety of interventions, participants and outcome measures.

This PhD research was undertaken in two PMSs in Nottingham, in the United Kingdom (UK). Before establishing the PMS, adults with CLBP were initially treated by their general practitioners (GPs). If treatment failed to improve patients' outcomes, then referrals to secondary care, which includes spinal surgery or rheumatology, might have been considered.

In the UK, the National Pain Audit, published in 2012, found that there are long waiting times for people with chronic pain to be referred to secondary care (27). This delay in treatment can increased the development rates chronic disabling back pain (28-31), which, therefore, increases the healthcare resource use and costs (32). Alongside the detrimental effects of treatment delay, there appears to be a high level of inappropriate spinal surgery unit referrals. Local data suggests that only 10% of people referred actually need a surgical consultation (33). Therefore, more targeted use of this service is needed in this patient group (34).

In the PMS, adults with CLBP have consultations with members of the multiprofessional team (including a pain consultant, a physiotherapist, a biopsychosocial practitioner and a nurse) for supported self-care management, or referral to community services, such as physiotherapy, or more specialist secondary care services. The community-based PMS facilitates access to a wide range of diagnostic and treatment pathways, such as magnetic resonance imaging (MRI), rehabilitation programmes and minor interventional procedures, such as trigger point injections. In addition, more complex surgical interventions can be offered if required (33).

Anecdotally, impressions are that people are benefiting from the new PMS and, if it were expanded, people in other localities would benefit from better pain management. However, financial constraints affect the possibility of expansion, or even of continuity, of the current service. Evidence so far from studies of other similarly designed interventions, suggests that PMS could be effective, although the effectiveness of the Nottingham PMS specifically is not known. Given that these types of services are costly and require integration between healthcare sectors, the effectiveness, patient acceptability and cost effectiveness of PMS need to be investigated before this model of care is more widely implemented.

Commissioners and decision makers need support to make decisions about service provision, so waiting for the full evaluative trial to be completed will not produce timely evidence to support decision making.

Therefore, the aim of this study is to carry out an evaluation of the PMS in Nottingham by conducting a service evaluation study to assess the patient characteristics and clinical outcomes of this service and also to generate data inputs for economic evaluation. In addition, in order to perform the economic evaluation of the PMS, a systematic review of cost effectiveness studies was needed to assess the quality of the published economic evaluations and to identify previously published decision analysis models that can be used to inform our study. Finally, an indicative economic evaluation was developed using the decision analysis model to compare the cost effectiveness of PMS with SC in managing CLBP, using data from the service evaluation study and published estimates of cost effectiveness.

1.2 Structure of the Thesis

Following this introduction chapter, five further chapters are presented in this thesis. The contents of each chapter are summarised below.

Chapter Two provides a review of the literature of the key areas that are addressed by this PhD: CLBP and management by PMS in terms of definition, evidence underpinning their effectiveness and cost effectiveness. Firstly, non-specific CLBP is defined, its epidemiology is presented and evidence around the personal and economic impacts is summarised and critiqued. The current recommendations for assessment of CLBP and its general management strategies, with a focus on the UK's recent National Institute for Health and Care Excellence (NICE) guidelines, are discussed. The challenges of managing CLBP and the important role of the biopsychosocial model in addressing these challenges are summarised here.

Secondly, the theoretical concept of the PMS in relation to the biopsychsocial model of pain are described. The evidence about the effectiveness and cost effectiveness of these services in managing CLBP is presented. The following section provides an overview of PMS in Nottingham and in the UK as a whole. Finally, the PhD study's justification, aim and objectives are presented.

Chapter Three is a prospective service evaluation study, which describes patient characteristics, outcomes and healthcare resource use for adults with CLBP referred to two PMS in Nottingham. It also aims to address the main methodological issues that might inform the design of future studies, including the recruitment rate and retention of patients, the feasibility of using health status measures and healthcare resource use diaries. The main findings are then compared with existing evidence. Finally, the chapter concludes by highlighting the strengths and limitations of the study.

Chapter Four is a systematic review, which aims to identify and critically appraise published economic evaluations of PMS for adults with CLBP. The search retrieved studies conducted from the time of the databases' inception to August 2017. The Cochrane Back Review Group (CBRG) risk of bias assessment tool and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) were used to assess the quality of the randomised controlled trials and the economic evaluations respectively. The chapter also aims to inform the design of the economic evalaution of PMS versus SC in Chapter 5.

Chapter Five presents an indicative economic evaluation of PMS versus SC in people with CLBP, using a Markov model based approach. The aim of this chapter was to

evaluate the lifetime cost effectiveness of PMS compared with SC in the management of people with CLBP from the UK NHS perspective. It also aims to quantify the uncertainty around the incremental costs and benefits of these services.

The model was designed and reported according to quality and reporting criteria and recommended approaches to ensuring model validity. Data from the service evaluation study in Chapter Three was combined with published estimates of effectiveness in a decision analysis model. Deterministic and probabilistic results are presented, followed by one-way sensitivity and scenario analysis. Finally, a discussion of the key findings, strengths and limitations is presented.

Chapter Six brings together the main findings emanating from the studies presented in the thesis (Chapters 3 to 5) and draws together recommendations in light of the existing evidence. The implications for policy, practice, people and research are presented, followed by the thesis conclusion.

Chapter 2

Literature Review, Aim and Objectives

2.1 Introduction

This chapter summarises the key research evidence and literature related to non-specific chronic low back pain (CLBP) and pain management services (PMS). It also recognises the limitations in both the literature and clinical practice. Finally, this chapter presents the justification for the study, with the main aim and objectives.

2.2 The Definition of Back Pain

The scope of this PhD is nonspecific CLBP. Non-specific low back pain is tension, soreness and/or stiffness between the lowest ribs and the inferior gluteal folds (1, 35, 36). The majority (approximately 90% to 95%) of people are diagnosed with nonspecific low back pain (37), with no recognisable cause or definite medical issues other than the pain itself.

Other spinal pathologies can cause low back pain, including cancer, cauda equina syndrome or infection (38). These conditions are very rare in primary care populations, accounting for 5% of cases (39-41). However, delayed or missed diagnoses can lead to substantial consequences for the patients. Therefore, clinicians need to be aware about red flags for major spinal pathologies, which include severe neurological deficit, history of cancer, night sweats, weight loss, age <20 years or >50 years (38). These conditions require immediate referral to specialist or emergency departments for prompt assessment and treatment. Given that the cause of these conditions is known and identifiable, the treatment pathways are also different than for nonspecific low back pain.

Low back pain is frequently classified based on symptom duration (14). Conventionally, nonspecific low back pain is categorised, according to its duration, as acute (<4 weeks), sub-acute (4-12 weeks) or chronic (>12 weeks) (14, 35). The International Association for the Study of Pain (IASP) describes acute low back pain as cramping or shooting, but it might be only dull or aching, worsened by movement. CLBP is generally aching, dull or burning (42). Acute pain is a result of tissue damage and is usually self-limiting, as the pain generally subsides when the damage is healed. On the other hand, chronic pain one that endures beyond the normal healing time and can be exacerbated by psychological factors (43, 44).

2.3 Natural History and the Clinical Course of Back Pain

Natural history is defined as the change in condition symptoms over time without treatment, whereas clinical course is the change in symptoms with the use of treatment (45). With regard to the natural history of back pain, the condition is considered self-limiting; 90% of patients experiencing low back pain recover in six weeks without any disability. However, in some cases, less severe pain might persist up to three months. Ongoing pain beyond three months is common, but does not definitely suggest a serious pathology (46).

Despite the self-limiting nature of back pain, a recurrence rate of up to 80% has been reported (47, 48). However, the factors that predict recurrence are still not clear (49). This suggests that the condition profile is highly variable. Data about the natural history of back pain is limited, as most of the patients with prolonged symptoms are offered some form of treatment (50).

The clinical course of back pain has been widely investigated (10, 11). These reviews have found that people with back pain achieve a rapid improvement in symptoms, which lasts for six months after treatment initiation, followed by a plateau. This trend of improvement is achieved regardless of the treatment provided; however, the effect size is highly variable as the patients' characteristics in the included studies, in terms of baseline pain intensity levels, were not comparable (11). This suggests that patients' characteristics can highly influence the treatment effect, which is backed up by recent evidence suggesting that illness perception and pain catastrophising are two major determinants of a poor prognosis (51). Moreover, other prognostic factors including not being in employment and having a high pain intensity level at baseline, were the strongest prognostic indicators for disability at one year in people with low back pain (52). Therefore, given the dissimilarities between CLBP and other back pain conditions, in terms of causes and treatments, these conditions are beyond the scope of this thesis.

2.4 The Epidemiology of Back Pain

In epidemiology, two terms are used to describe the spread of a disease or a condition, which are incidence and prevalence. Incidence is defined as the rate at which new cases arise in a population during a specified period, whereas prevalence is defined as the proportion of a population that are cases at a point in time (53). In low back pain, it is difficult to estimate the incidence as first- episodes of low back pain are already high by early adulthood and the condition has a recurring clinical course (54).

CLBP prevalence was 19.6% worldwide (2) whereas, in the UK, the prevalence was 11% (55). The Health Survey for England, published in 2011, (56) randomly surveyed 8,992 people, which was considered to be a representative sample of the UK population. The survey found that CLBP was the second most commonly reported site of pain, with more women than men suffering from this type of pain (44 % compared with 37%).

2.5 The Personal and Economic Burden of Back Pain

Disability adjusted life years (DALYs) is a term used to measure the burden of disease (57). DALYs is defined as the sum of years lived with disability. CLBP has a significant effect on physical function, psychological wellbeing and quality of life, which can lead to disability (3-5).

According to the Global Burden of Disease Study 2010 (6), CLBP was the 3rd leading cause of disability adjusted life years (number of DALYs per thousand = 3181, %DALYs=3.9), after ischaemic heart disease (number of DALYs per thousand = 7850, %DALYs=9.6) and COPD (number of DALYs per thousand = 3659, %DALYs=4.5).

The economic burden is also substantial. People with CLBP are regarded as great utilisers of healthcare resources (58-62). Three types of costs are usually used in cost of illness studies: direct medical, direct non-medical and indirect costs (63). Direct medical costs are those directly associated with medical interventions or health services, such as GP visits and pain medicines. Direct non-medical costs are the out-of-pocket expenses incurred by people or families, such as travel costs. Indirect costs

are those incurred due to productivity loss, such as time off work or early retirement due to illness.

In 1998, a UK study stated that the societal cost of CLBP. in terms of healthcare resource use and work absence periods, was more than £12 billion (61). This cost involved £1.6 billion incurred in providing direct healthcare resources, which include primary and secondary care visits, £1.6 billion associated with direct non-medical costs, which include informal care, and £9.1 billion related to productivity losses.

A more recent study in the UK (62) was conducted to assess the one-year healthcare costs associated with the management of CLBP within the UK NHS using the UK Clinical Practice Research Database (CPRD). People with CLBP were identified for the study period (January 1, 2007 to December 31, 2009) using diagnostic records (n=64,167) and matched to people without CLBP (n=52,986) based on age, sex and the general practitioners' (GP) clinical settings. The study revealed that healthcare resource utilisation for people with CLBP was double that of the matched controls (£1074 vs. £516; $P < 0.05$). Fifty eight percent of this cost was accounted for by GP consultations, 22.3% by referrals to secondary care and the rest by pain medicines. In the United States (US), the direct and indirect costs in 2013 were $23.4 billion (64) and $25.6 billion (65) respectively (66).

The cost of illness for CLBP has been studied extensively worldwide. A systematic review conducted by Dagenais et al. aimed to study the cost of illness in the US and internationally (60). The systematic review identified 21 studies from Japan, Korea, Australia, Belgium, the Netherlands, Sweden, the UK and the US.

In this systematic review, the direct cost of CLBP represented 11% to 66% of the total costs. The largest mean direct cost components for CLBP were physiotherapy (17%) and inpatient care (17%), followed by pharmacy services (13%), primary care (13%) and outpatient services (8%). Among the studies calculating estimates of total costs, indirect costs resulting from loss of work productivity represented 55% to 89% of the total costs related to CLBP.

In order to value productivity loss among employees, the “human capital approach” and the “friction cost method” can be used (67). In the human capital approach (68), all production not performed by an individual due to illness is considered as production loss, whereas, in the friction cost method, production loss is limited to the “friction period”, which is the duration required to replace the sick worker and to train a new one. The use of these methods has been strongly argued in health economics (68) and both methods have limitations. The human capital approach might overestimate the value of production loss, especially in the case of a long period of absenteeism. On the other hand, the friction cost method considers leisure time to be “valueless”.

In this review, the human capital approach was used to assess the indirect costs in 7 studies, whereas the friction cost method was used in 4 studies; the remainder of the studies did not report the productivity valuation method. Despite heterogeneity in methodology producing a wide range of cost of illness estimates, it was clear that CLBP represented a substantial economic burden.

The economic burden of CLBP is also substantial when compared with other musculoskeletal conditions, including fibromyalgia, ankylosing spondylitis and

rheumatoid arthritis (69-71). When comparing CLBP with fibromyalgia and ankylosing spondylitis (69), the total cost per patient per year for CLBP was €8533, whereas for fibromyalgia and ankylosing spondylitis the costs were €7814 and €3205 respectively.

In people with CLBP and rheumatoid arthritis in Sweden, the total cost per patient was €23,755 and €12,286 respectively (70, 71). In CLBP the direct medical cost accounted for 15% of the total cost, whereas, in rheumatoid arthritis, it was 41%; the remainder was for indirect costs.

2.6 The Assessment and Management of CLBP

A recent systematic review, which aimed to investigate the impact of CLBP, showed that it affects several life domains (5). People with CLBP report limitations in daily activities (72-74), such as housework and leisure activities. Moreover, CLBP was found to affect relationships, promoting feelings of loneliness, cohabitation problems, concerns surrounding sexual relations and reduced social interaction (75, 76).

According to the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) group (77), outcomes need to be evaluated based on their validity, reliability and responsiveness (78). Validity is typically defined as the degree to which a tool measures what it is intended to measure. Reliability is focused on the consistency of the instrument over repeated uses. Responsiveness, also known as "sensitivity to change", is a measure of how well an instrument can identify changes as a consequence of an intervention.

Several outcome initiatives with special focus on chronic pain in general (77, 79), and on low back pain (80-83), agreed that pain intensity and physical functioning are essential domains that need to be considered when assessing patients with CLBP. Other domains, including emotional functioning (77), patients' satisfaction (82, 83), global improvement (77) and quality of life (80, 82, 83) were also recommended by some initiatives as a core domains that need to be considered for assessment.

Consequently, large number of health status measures are available to assess the treatment of CLBP for routine practice or research. These health status measures can be broadly classified into: physical function, pain intensity, psychological, generic quality of life and preference-based outcomes (84).

Given that CLBP can cause disability that significantly affects the quality of life, a cost utility analysis that uses quality adjusted life years (QALY) is the preferred type of economic evaluation that should be performed when assessing CLBP interventions (85). In the UK, NICE has recommended that incremental cost per QALY should be reported in all health technology assessments (HTAs) (86). Using incremental cost per QALY enables a standardised approach to comparing economic evaluation across different healthcare interventions.

Preference based outcome measures, including the EuroQol 5 dimensions 3-level (EQ-5D-3L) (87, 88), the EuroQol 5 dimensions 5-level (EQ-5D-5 L) (89) and the six-dimensional health state short form (SF-6D) (90), can be used to generate QALYs and to perform cost utility analysis (85). Recently , NICE has endorsed the use of the EQ-5D-3L as the preferred measure for economic evaluations (91).

The description and the psychometric properties for the most commonly used health status measures in CLBP are summarised in Table 2-1.

Table 2-1 Psychometric properties for the commonly used health status measures in CLBP (84)

Domain	Measure	No. items	Valid	Reliable	Responsive
Function	Oswestry Disability Index (ODI) (92)	10	√	√	√
	Roland Morris Disability Questionnaire (RMDQ) (93)	24	√	√	√
Pain intensity	Numeric Pain Rating Scale (NPRS) (94)	11	NT	NT	√
	Visual Analogue Scale (VAS)	1	?	√	NT
	Brief Pain Inventory (BPI) (95, 96)	14	√	NT	NT
	Pain Disability Index (PDI) (97)	7	ND	√	NT
Psychological	Fear Avoidance Belief Questionnaire (98)	16	√	√	Low responsiveness
	Tampa Scale for Kinesiophobia (99, 100)	17	√	√	√
	Beck Depression Inventory (101)	21	√	√	NT
Generic/QoL	Short Form 36 (102)	36	√	√	√
	Nottingham Health Profile (103)	38	√	√	NT
	Short Form 12 (104)	12	√	√	NT
	Sickness impact profile (105, 106)	136	√	√	NT
Preference based outcome	EuroQol 5 dimensions 3-level (87, 88)	5	√	NT	√
	EuroQol 5 dimensions 5-level(89)	5	NT	NT	NT
	Short Form 6 (90)	12 or 36	NT	NT	NT
NA indicates not applicable; ND, no data; NT, not tested, ? Questionable					

2.6.1 Treatment Overview

Many treatment options are available to manage CLBP (107), which include a wide range of pharmacological treatments, including non-steroidal anti-inflammatory drugs (NSAIDs), opioids, tricyclic antidepressants and muscle relaxants. Other non-pharmacological modalities, including physiotherapy, cognitive behaviour therapy and pain management services based on a cognitive approach, might also be effective.

The American College of Physicians (ACP) and the American Pain Society (APS) have recently published two systematic reviews aimed at assessing the effectiveness of pharmacological and non-pharmacological treatment for CLBP (108, 109) The outcome measures used to assess the effectiveness of these treatment modalities included pain intensity measured by NRS or VAS and functional disability measured by RMD or ODI. The magnitude of effect (effect size) was classified as small (standardised mean difference (SMD) =0.2-0.5), moderate (SMD=0.5-0.8) or large (SMD >0.8) (110, 111). In addition, the strength of evidence for each treatment was assessed using criteria developed by the US Preventive Service Task Force (USPSTF) for RCTs (112) and A Measurement Tool to Assess Systematic Reviews (AMSTAR) for systematic reviews (113). The strength of evidence was classified as insufficient, low, moderate and strong based on these tools. Treatments that have a small to moderate effect on pain and functional disability are listed in Table 2-2.

Table 2-2 Effectiveness of Pharmacologic and Nonpharmacologic Treatments for chronic low back pain

Treatment	Pain intensity		Functional disability	
	ES	SOE	ES	SOE
Pharmacological treatment				
NSAIDs*	Small to moderate	Moderate	None to small	Low
Opioid (strong)	Small	Moderate	Small	Moderate
Opioid (buprenorphine patch or sublingual)	Small	Low	Unable to estimate	Insufficient
Tramadol	Moderate	Moderate	Small	Moderate
Antidepressants: duloxetine	Small	Moderate	Small	Moderate
Non-Pharmacological treatment				
Exercise vs. UC	Small	Moderate	Small	Moderate
Motor control exercise s vs. minimal intervention	Moderate	Low	Small	Low
Tai chi vs. waiting list or no tai chi	Moderate	Low	Small	Low
Yoga vs. usual care	Moderate	Low	Moderate	Low
Yoga vs. education	Small (ST) No effect (LT)	low	Small (ST) No effect (LT)	Low
Mindfulness-based stress reduction vs. UC or education	Small	Moderate	Small	Moderate
Progressive relaxation vs. wait-list control	Moderate	Low	Moderate	Low
Electromyography biofeedback vs. wait list or placebo	Moderate	Low	No effect	Low
Cognitive–behavioural therapy vs. wait-list control	Moderate	Low	No effect	Low
Multidisciplinary rehabilitation vs. UC	Moderate (ST) Small (LT)	Moderate	Small (ST and LT)	Moderate
Acupuncture vs. sham acupuncture	Moderate	Low	No effect	Low
Acupuncture vs. no acupuncture	Moderate	Moderate	Moderate	Moderate
Spinal manipulation vs. inert treatment	Small	Low	-	-

* Drugs were compared with placebo, ES= effect size, SOE= strength of evidence, UC= usual care, ST= short term, LT=long term, RCT=randomised controlled trial, SR=systematic review.

Only two medicines have a moderate effect on pain intensity, which include NSAIDs and tramadol, whereas their effect size on functional disability was small.

On the other hand, a wide range of non-pharmacological modalities have a moderate effect on pain intensity, including motor control exercise, Tai chi, yoga, progressive relaxation, electromyography biofeedback, cognitive behavioural therapy, multidisciplinary treatment and acupuncture. Among those treatments, only yoga, progressive relaxation and acupuncture appear to have a moderate effect on functional disability. However, the strength of evidence underpinning the use of motor control exercise, Tai chi, yoga, progressive relaxation and electromyography biofeedback was low.

Multidisciplinary treatment was the only treatment that had a moderate effect on pain intensity and a small effect on functional disability and was supported by moderate quality evidence. In addition, it was only treatment that has been assessed for its long-term effectiveness (12 months) on pain intensity and functional disability.

Given that these services can include a wide range of pharmacological and non-pharmacological treatments, evidence is needed to assess the types of treatments provided in these services and their long-term effects on pain intensity and functional disability.

2.6.2 Chronic Low Back Pain Guidelines

The NICE guidelines for CLBP and sciatica were recently updated, in 2016 (13). This guideline is based on the best available evidence from systematic reviews, with explicit

focus on cost effectiveness. Where evidence about a certain treatment is lacking, opinion from the guideline development group was considered.

The guideline recommends using a risk stratification strategy, such as the STarT Back risk assessment tool (114), upon initial patient contact with the healthcare practitioner, to inform shared decision making regarding a stratified treatment approach. Based on this stratification, people who are at a higher risk of poor prognosis should receive intensive and complex management, whereas people with a better prognosis should be offered simpler and less intensive support.

According to the NICE guidelines, information and advice to support self-management should be offered to all people presenting with CLBP. Exercise programmes and pharmacological treatments, including NSAIDs, or weak opioids if NSAIDs are contraindicated, are recommended. Manual therapy or psychological therapies using a cognitive behavioural approach, or both, are only indicated as part of a treatment package including exercise.

People with substantial psychological distress, or if previous treatments have not been effective, should be referred to combined physical and psychological treatment programmes that incorporate a cognitive behavioural approach. These services are also defined as “pain management services” (PMS) (115). Finally, radiofrequency denervation is recommended for people who have failed to respond to previous treatments and for those having neurological involvement with severe localised pain.

The guidelines do not recommend several pharmacological therapies and treatment modalities, which include paracetamol alone, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, anticonvulsants, traction, orthotics, spinal injections, disc replacement and spinal fusion, due to insufficient evidence.

In this guideline, the use of manual therapy or psychological therapies, or both, were underpinned by high quality evidence from RCTs. Recommendation against the use of acupuncture was also supported by high quality evidence. Moderate quality evidence from RCTs supported the use of NSAIDs, combined physical and psychological treatment programmes and radiofrequency denervation. Recommendation against the use of strong opioids was also supported by moderate quality evidence. Low quality evidence from RCTs supports risk stratification, whereas the guideline development group opinion supports the use of weak opioids.

Over recent months, updated guidelines have been published by the ACP in the US (14). Generally, there was an overall agreement between the two guidelines to favourably recommend non-pharmacological treatment modalities (13, 14). However, there are dissimilarities in the inclusion of a treatment into a guideline; for example, acupuncture is excluded from NICE guidelines (13) but is an option in the ACP guidelines. Opioid use for back pain is still a challenging issue in both guidelines. The most remarkable difference between the guidelines is that the NICE guidelines do not recommend using strong opioids at all and weak opioids should be used only if

NSAIDs are contraindicated, whereas the ACP guideline recommends using strong opioid if NSAIDs, duloxetine and tramadol fail to improve patients' outcomes.

2.6.3 Cost effectiveness of CLBP treatments

The cost effectiveness of pharmacological and non-pharmacological treatments for back pain have been investigated (116-118). Haas et al. included seven studies assessing pharmacological interventions for back pain (116). The treatment included epidural injections (119-121), implantable drug delivery systems (122), pregabalin (123) and duloxetine (124, 125). In this review, only two studies consisted of economic evaluations using decision analysis models (124, 125), the remainder were economic evaluations alongside RCTs (119-123). The methodological quality of the economic evaluation was assessed using the Quality of Health Economic Studies (QHES) (126). In this review, useful conclusions about the cost effectiveness of pharmacological treatment can be drawn for duloxetine and pregabalin only. This due to the lack of supporting evidence for the use of epidural injections and implantable drug delivery systems, according to recent clinical practice guidelines (13, 14). In addition, the methodological quality of the included studies was not high, except for studies assessing the cost effectiveness of duloxetine (124, 125). The strength of these studies was attributed to the source of effectiveness data and the implemented modelling technique. However, recent guidelines also do not recommend using duloxetine to manage people with CLBP (13, 14).

In economic evaluations, the study perspective determines which costs are relevant in a particular economic evaluation, as it refers to the viewpoint from which the cost is

incurred (63). The widest perspective is from a societal perspective, which includes all types of costs. In this systematic review, studies assessing duloxetine were conducted from a private payer perspective, where societal cost are not incurred. Therefore, the effect of duloxetine from a societal perspective is still unknown.

Following this systematic review, an economic evaluation that aimed to assess the cost effectiveness of NSAIDs compared with opioids was conducted (117). The study found that NSAIDs were cheaper and more effective in terms of QALY gain compared with opioids. The probability of NSAIDs being cost effective was 57% at all willingness to pay thresholds. NSAIDs are recommended in both guidelines as the 1st line pharamcolgical treatment for CLBP (13, 14). However, this study was also undertaken from a private payer perspective, which impedes informative conclusions about the cost effectiveness of this medicine class from a societal perspective.

Apart from pharmacological treatments, a systematic review for the cost effectiveness of non-pharmacological and non-invasive interventions in back pain has been published recently (118). This systematic review included 33 studies and the interventions were classified into combined physical exercise and psychological therapy interventions, physical therapy interventions, education interventions and manual therapy. Only two studies were economic evaluations using decision analysis models; the remainder were alongside RCTs. The methodological quality of the economic evaluation was assessed by using the Consensus on Health Economic Criteria (CHEC) list (127).

The systematic review found that combined interventions showed non-significant increases in QALYs and slightly increases in costs compared with the control, whereas the studies assessing physical therapy interventions were inconclusive.

Interventions that included a patient education and information component seem to reduce productivity loss, which balances the small increment in costs. Finally, studies assessing manual therapy found that this intervention is cost effective compared with usual care but only over the short term (12 months post intervention).

In this review (118), the authors included low back pain regardless of the duration. Therefore, it is not possible to extrapolate the results of this review to CLBP. A comparison between the results of these systematic reviews (116, 118) and within different types of intervention is not possible for several reasons. Firstly, the reviews included several types of economic evaluation, which include cost effectiveness analysis (CEA), cost utility analysis (CUA) and cost benefit analysis (CBA). The outcomes in these analyses are different as the CEA use natural units such as reduction in disability or number of working days lost as an outcome, whereas CUA uses quality adjusted life years (QALYs) as a generic outcome. CBA expresses the outcomes as a monetary value. This makes a comparison problematic.

Secondly, the adopted perspectives in the included studies were variable, which means that the types of costs incurred in each study were different. This is of particular importance if the condition has a high loss of productivity, which significantly affects indirect costs. Thirdly, the methods of collecting healthcare resource use and unit costs were also variable and poorly reported, with this variability also depending on the

adopted perspective. Fourthly, the time horizon or the length of follow up was short (mean duration 12 months) and this duration is insufficient in determining the long term effect of the intervention on costs and benefits. Finally, given that the vast majority of the economic evaluations were alongside RCTs, the authors of these reviews did not assess the methodological quality of the these RCTs which is essential in assessing the strength of the economic evaluation.

2.7 The Biopsychosocial Model and Pain Management Services

CLBP is a challenging condition and possible reasons for this are its unknown pathophysiological aetiology and heterogenous clinical course (128). Secondly, most spine care experts agree that CLBP is a physical problem that might be exacerbated by a wide range of socio-demographic and psychosocial factors, which include, but are not limited to, occupation and educational level, previous history of CLBP and psychological illness, including depression (12, 128).

As a result of this challenge, the biopsychosocial model has emerged as the most valid framework in understanding and managing CLBP (12, 129). The model addresses pain as a complex and dynamic interaction between physiological, social and psychological elements. This approach has replaced the old biomedical model (16), which focuses mainly on the physiological component of the pain process with limited emphasis on patient responses and behaviour towards pain.

This has led to the design of services to address these multiple domains, classically involving a combination of psychological, physical and educational elements and often provided by a team of healthcare professionals with different qualifications (130).

2.8 Pain Management Service Terminology

Terms such as “multimodal”, “multicomponent”, “multidisciplinary” and “interdisciplinary” are often used to describe pain management services in the literature (115, 131, 132). Multidisciplinary services have been defined by Choi et al. (115) and Gatchel et al. (131) as the involvement of several healthcare professionals in providing patient care. However, the level of coordination and the communication between staff might be limited as these individuals might be not working in the same facility or setting. Another term that was defined by Choi et al. (115) and Gatchel et al. (131) is the “interdisciplinary” service, which means that healthcare providers work in a coordinated manner “under one roof”, with frequent communication, to provide patient care.

On the other hand, the International Association for the Study of Pain (IASP) (133) defined multidisciplinary pain services as a variety of healthcare professionals working in a collaborative and coordinated manner to provide patient care.

Despite the clear distinction reported by Choi et al. (115) and Gatchel et al. (131), “interdisciplinary” and “multidisciplinary” are being used interchangeably (131) possibly due to the opposing IASP definition (133).

Historically, in the UK, pain services development has been informed by the IASP guidance. With the NHS reconfiguration and the transfer of the management of long-term conditions back into community service, the Royal College of General Practitioners (RCGP) produced guidance (Pain Management Services: Planning for the Future) for Clinical Commissioning Groups (CCG) (134) that moves away from

the IASP towards a pain management model that is best delivered by a multi-professional team. The guidance named the service as a “pain management service” and the terms “multi-professional” and “multidisciplinary” were used as synonyms to describe the variety of professionals in the team rather than the integration between them. Therefore, in this thesis, following the RCGP guidance, the pain management service (PMS), which fulfills the multidisciplinary pain management service, was used to define the service in the UK.

2.9 Effectiveness and Cost Effectiveness of PMS in CLBP

A systematic review was undertaken by Kamper et al. to study the effect of PMS on clinically relevant outcomes in CLBP (15). These services were descibed as multidisciplinary, in which health services targeting at least two of the social, physical, psychological and/or occupational aspects were provided by healthcare professionals from at least two different clinical qualifications. These services can be delivered in primary, secondary or tertiary care.

Published RCTs targeting adults with CLBP that compared PMS with standard care, physical treatment, surgery and waiting lists were included. Outcome measures included pain intensity and functional disability. Pain intensity was measured using visual or numerical scales and disability was assessed using the Roland Morris disability scale. Pain intensity and functional disability are two essential domains of the assessment of pain and have been recommended by the IMMPACT group (77).

Forty-one studies published between 1989 and 2012 were included in the systematic review. Thirty-three studies were conducted in Europe, three were from the US, three

were from Iran and two studies were from Australia. A total of 6858 participants were included. The average age range was between 40 and 45 years old and gender balance was varied. Thirty-three studies reported low baseline symptom intensity (less than 60% on the pain intensity and disability scales), whereas four studies reported high baseline symptom intensity; the remainder did not provide sufficient data to categorise baseline symptom intensity.

Sixteen of the 41 studies compared PMS with SC. For the disability measure, the standardised mean difference (SMD) ranged between 0.41 (95% confidence interval (CI) 0.62-0.19) to 0.23 (95% CI 0.06 to 0.4) over three and 12 months respectively. For pain intensity, the SMD ranged between 0.55 (95% CI 0. to 0.) and 0.21 (95% CI 0.04 to 0.37) over three and 12 months respectively. Pooled estimates from these studies provided moderate quality evidence that PMS are more effective, compared with SC, in reducing disability and pain intensity. The authors of this systematic review suggested that PMS might be considered a plausible option for managing CLBP in adults with substantial psychosocial risk factors (15).

A literature review was performed to update the results from Kamper et al. Few RCTs have been published between 2014 and 2017 (135-139). One study has been conducted in Europe (135) and one study has been carried out with multiple follow up periods in Iran (137-139). The comparators in these studies were exercise (135) and drug therapy (137-139). The study assessing the effectiveness of PMS compared with exercise used the Oswestry Disability Index (ODI) to measure disability (135) and found that the intervention was significantly more effective in reducing disability (mean difference

in ODI = 9.9 (95% CI 11.6 to 8.2) five weeks after the intervention. The effect of the intervention remained sigficantly effective over two years (mean difference in ODI = 17 (95% CI 18.5 to 15).

Tavafian et al. assessed the PMS compared with drug therapy at 12 months (137), 24 months (138) and 30 months (139). The PMS model in this study includes a physiotherapist, a rheumatologist, a health education specialist and a psychologist. Each patient received five sessions, followed by monthly booster sessions and monthly telephone counselling, to encourage the participants to maintain the acquired skills. The study found that the intervention was more effective compared with drug therapy (P = 0.02) in improving the physical functioning domain in the SF-36 scale at 12 months post PMS (137). At 24 months post intervention, the intervention was more effective (P = 0.01) in improving the mental health domain in the SF-36. Finally, at 30 months, the intervention was more effective in improving the mental health domain (P = 0.01). Although previous RCTs assessed the effectiveness of PMS, comparative studies with SC were lacking. The PMS in Tavafian et al.'s study is also not comparable with the practice in the UK and in Nottingham. The details of the Nottingham PMS are discussed in section 2.12.

Recently published NICE and ACP guidelines for CLBP (13, 14) recommend the use of PMS that are based on the cognitive behavioural approach. Both guidelines suggest that these services have a moderate effect on pain intensity compared with SC. This recommendation was based on the moderate quality evidence derived from the meta analysis by Kamper et al. (15).

A small number of cost effectiveness studies of PMS have been undertaken in Europe (20, 21, 25, 26, 140) and others are still ongoing in Spain and the Netherlands (23, 141). Given that these services are resource intensive (16), evidence is needed to demonstrate the cost effectiveness of PMS for people with CLBP by conducting a systematic review to summarise and critique the quality of the economic studies. This systematic review is discussed in Chapter 4.

2.10 Pain Management Services in the UK

The National Pain Audit, published in 2012 (27), reported that each PMS covered between 200,000 and 370,000 people in the UK. A total of 204 services participated in the audit; however, the actual number of PMS within the UK is not known. These services mainly receive people with musculoskeletal pain, many of whom are of working age (27). The mean number of new and follow-up appointments were, respectively, 35 and 21 per service per month (142), with people usually having been referred by their GP or consultant (143).

Over recent years, national reports, such as the Chief Medical Officer (CMO), the National Pain Audit and Health Survey for England (HSE) and English Pain Summit reports have focused on chronic pain management, describing its impact on people and highlighting necessary areas for improvement (27, 56, 144, 145).

These reports have revealed that the limited number of specialist pain services around the country are overwhelmed with referrals and that only 14% of people with pain have seen a pain professional (144). Data from the National Pain Audit, published in 2012, concluded that there was a great variation in access to PMS across the UK. The English

Pain Summit, held in 2011 (145), reached similar conclusions, agreeing that many of those living in pain are denied the benefit of appropriate management and improved outcomes due to the patchy commissioning of services. The systems and infrastructure appear to be inadequate to meet patient needs or demands.

In the US, substantial disparity in chronic pain management also exists (131). Despite the early success of PMS in the last decade, their development was slow, mainly due to insufficient provision to support the high initial costs of launching a PMS, the lack of sufficient time to organise and train the healthcare staff providing the service and the lack of a unifying model of pain management care that serves as a directing strategy for integrating the numerous PMS (146).

2.11 Literature Review Summary

This literature review highlights that CLBP is a challenging condition, associated with substantial personal, economic and societal burdens. In order to address the complex nature of CLBP, PMS are needed. The evidence from systematic reviews and clinical guidelines suggests that PMS are effective in managing CLBP. However, the quality of evidence supporting the use of these services was moderate. Despite the national awareness of the inconsistent commissioning of pain services and the increasing prevalence of CLBP in the UK, no previous cost effectiveness studies have evaluated the PMS for people with CLBP in the UK.

2.12 PMS in Nottingham

The service in Nottingham is an example of a PMS spanning primary and secondary care. The main aim of this service is to reduce inappropriate referrals to secondary care and to facilitate patient access to a comprehensive assessment of a wide range of musculoskeletal and other pain conditions, with patient-tailored specific treatment plans developed by a pain management consultant (33).

This PhD project was conducted in the community served by the Nottingham West Clinical Commissioning Group (NWCCG) and the Newark and Sherwood CCG. The NWCCG is made up of 12 practices, with approximately 93,600 people, and Newark and Sherwood CCG is made up of 16 practices and 150,000 patients.

The PMS in Nottingham takes referrals directly from GPs, with people referred to a dedicated pain management pathway (33). A consultant in pain medicine leads the service and a team including a physiotherapist, a biopsychosocial practitioner and a nurse, which operates out of four practices in NWCCG, supports him. An individualised pain management plan is formulated and agreed with each patient. People might then have consultations with members of the team for supported self-care management, or community services, such as physiotherapy, or more specialist secondary care services. Although this service provides many treatment modalities, the approach is individualised based on the patient's needs. A description of the Nottingham PMS is illustrated in Figure 2-1.

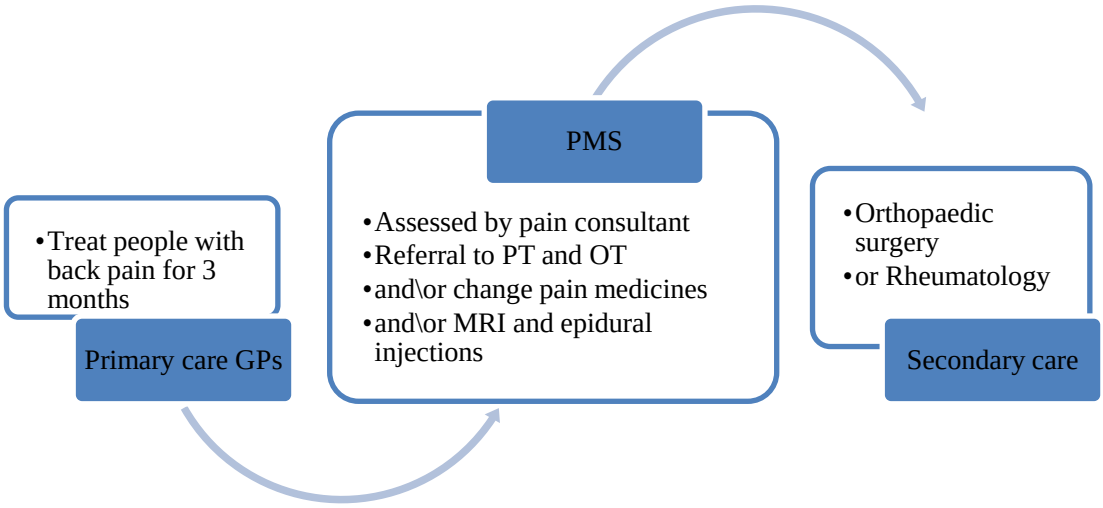


Figure 2-1 Description of the PMS in Nottingham

The pain management pathways address musculoskeletal and spinal pain, fibromyalgia and neuropathic pain. There is a quick access to magnetic resonance imaging (MRI), rehabilitation programmes and minor interventional procedures, as well as more complex surgical intervention via a virtual spinal clinic with secondary care partners if required.

Before establishing the PMS in Nottingham, people with CLBP were treated by their GPs. If treatment failed to improve patients' outcomes, their GP referred them to the secondary care spinal unit or to other services, such as rheumatology. After assessment by secondary care consultants, some people were eligible for surgery but most of them were referred back to their GPs. The PMS and SC pathways are fully described in Chapter 5.

2.13 Study Justification

In the UK, the National Pain Audit surveyed 9,588 people attending 204 PMS across the UK (27). The audit found that there was a long waiting time for people with chronic pain to be referred to secondary care (27). The audit found that 25% of patients had waited more than five months for an appointment with the PMS. In a UK study assessing the referral patterns between primary and secondary care, it was found that 36% of people with musculoskeletal pain were waiting for more than one year after referral to orthopaedic or rheumatology departments in secondary care (147).

In back pain, the long waiting time has a deteriorating effect on psychological wellbeing and quality of life. Evidence suggests that the sub-acute phase (4-12 weeks from initial presentation) is a critical period, as psychosocial factors progressively become more important in the development of pain as a chronic condition. Maladaptive thoughts and behaviours at twelve weeks seem to be associated with a change from acute to CLBP (28-31), which, therefore, increases the healthcare resource use and costs (32).

Alongside the detrimental effects of treatment delay, there appears to be a high level of spinal surgery unit referrals for people with CLBP where surgical intervention is ultimately not indicated. The local data from Nottingham found that only 10% of people referred to secondary care needed a surgeon consultation (33). A higher number of inappropriate referrals were reported by Speed et al. (147), whose study showed that only 42% of orthopaedics referrals were listed for a surgical procedure and that the remainder were considered to be inappropriate. This suggests that more targeted use

of this service is needed (148). As a result of the limitations in the standard care pathway of managing chronic pain, the Nottingham West and Newark and Sherwood PMS were established in 2008 and 2013, respectively (33).

Anecdotally, the impressions from the Nottingham CCG commissioners are that people are benefiting from this service and, if it were expanded, people in the Nottingham area (and the East Midlands more generally) would benefit from this treatment pathway. However, in Nottingham, as in other parts of England, financial constraints define the possibility of expanding, or even the continuity of, the current service.

Commissioners and decision makers need support to make decisions about service provision, so waiting for the full evaluative trial to be completed will not produce timely evidence to support decision making. It has long been recognised that economic evaluation should be iterative, generating progressively more precise estimates of cost-effectiveness and helping to maximise the efficiency of healthcare research and development, while still allowing the best evidence available at any one time is essential to support decision-making (149).

The paucity of economic evaluations of PMS and the variable levels of evidence underpinning the effectiveness of these services suggest that cost effectiveness studies need be conducted before this model of care is more widely implemented. Therefore, the aim of this study is to carry out an evaluation of the PMS in Nottingham by conducting a service evaluation study to assess the patient characteristics and clinical outcomes of this service and also to generate data inputs for the economic evaluation.

In addition, in order to perform the economic evaluation of the PMS, a systematic review of cost effectiveness studies was needed to assess the quality of the published economic evaluations and to identify previously published decision analysis models that could be used to inform our study. Finally, an indicative economic evaluation using a decision analysis model was developed to compare the cost effectiveness of PMS with SC in managing CLBP using data from the service evaluation study and published estimates of cost effectiveness.

2.14 Methodology Justification

The UK's Medical Research Council (MRC) defined complex interventions as those that address "...behaviours, parameters of behaviours (e.g., frequency, timing), and methods of organising and delivering those behaviours (e.g., type(s) of practitioner, setting and location)" (150). Based on the MRC defintion, the PMS can be considered a "complex" intervention. This complexity is as a consequence of the number of interacting components within the service and the variety of intended outcomes (150). The integration of different managerial, organisational and clinical levels further enhances the complexity of management (151). The assessment of the effectiveness of these services needs to be developed carefully, due to the multidimensional nature of pain and its consequences in terms of outcome measures, which include pain intensity, functional disability and quality of life (128). There are known difficulties and methodological challenges in evaluating complex interventions. The Medical Research Council (MRC) published a framework that recommended evaluating complex interventions through observational and developmental work, followed by an

exploratory trial, before conducting the definitive evaluation. This is required to identify key uncertainties in the design and assessment of the intervention and its evaluation (150).

2.15 Aim and Objectives

The overall aim of this thesis was to describe the characteristics, treatment pathways, outcomes and healthcare resource use of people with CLBP managed by PMS in Nottingham and to generate an indicative estimate of cost effectiveness. The objectives of this thesis were to:

1. Describe the demographic characteristics of people with CLBP and their treatment pathways in the PMS in Nottingham.

2. Determine the patient outcomes and healthcare resource use of the PMS using patient reported outcome measures and healthcare resource use.

3. Assess the feasibility of recruitment and performance of study procedures.

4. Summarise and critique economic evaluation studies assessing PMS for the management of people with CLBP.

5. Derive indicative estimates of cost effectiveness of PMS compared with SC in managing CLBP, using published estimates of effectiveness and cost.

6. Inform the design of a future randomised trial to evaluate the effectiveness and cost effectiveness of PMS.

Chapter 3

Describing the Characteristics, Treatment Pathways, Outcomes and Healthcare Resource use of People with Chronic Low Back Pain Managed by the Pain Management Service in Nottingham: A Service Evaluation Study

3.1 Introduction

Complex interventions, including community-based pain management services (PMS) are being widely implemented in clinical practice. A rigorous evaluation, based on the Medical Research Council (MRC) for evaluating complex intervention, is needed to determine their effectiveness (150). According to the MRC guidelines, a service evaluation study is required to assess patients' recruitment and retention. In addition, the feasibility of collecting data in real practice, which is considered a challenging task, needs to be tested before conducting larger trials.

The aim of this chapter is to describe the characteristics of people with chronic low back pain (CLBP) who attend a PMS in Nottingham, their outcomes and healthcare resource use.

Objectives:

1. Describe the demographic characteristics of people with CLBP.

2. Determine the clinical outcomes of people with CLBP attending the PMS using patient-reported outcome measures at baseline, three months and six months following PMS referral.

3. Obtain healthcare resource use for people managed by the PMS from the perspective of the NHS using patient-reported healthcare resource use during the six months following referral.

4. Assess the feasibility of recruitment and performance of study procedures.

3.2 Method

3.2.1 Study Design and Setting

This was a prospective cohort study using patient level data. The study is in the primary care setting served by Nottingham West Clinical Commissioning Group (NWCCG) and Newark and Sherwood Clinical Commissioning Group (NSCCG). NWCCG is made up of 12 practices and approximately 93,600 patients, while NSCCG is made up of 16 practices and approximately 150,000 patients.

3.2.2 Sample Size and Justification

As this was a service evaluation study, a sample size calculation was not required to derive an effect size. However, the sample obtained in this study provides data to inform a future sample size calculation. The largest sample possible is required to provide richer information about the patient cohort using the PMS for back pain. The number was based on the time and resources available.

According to the PMS annual report (personal communication with Dr. Kelvin Lim), the number of people with CLBP referred to both services is around 800 people per year. The intended duration of patient recruitment is 9 months, to ensure that the maximum number of particiants are being approached and recruited. Given this recruitment period, the sample estimate was up to 600 patients.

3.2.3 Inclusion Criteria

People were included if they met the following criteria:

1. Adults (18 years or older), attending the PMS for the first time and who have had non-specific CLBP.

2. Participants were required to have basic literacy skills and to be able to understand and consent to the study.

3.2.4 Exclusion Criteria

People were excluded if they met the following criteria:

1. Having a specific pathology for back pain, such as an infection or cancer.

2. Having had a spinal surgical procedure in the past six weeks, or having to undergo surgery within three months.

3. Having a severe psychiatric disorder, such as major depression or psychosis.

4. Being pregnant or having given birth in the past three months.

5. Being unable to complete questionnaires written in the English language.

3.2.5 Health Status Measures

The health status measures used in this study were the key health status measures affected by the presence and management of CLBP. The primary outcome was a change in functional disability measured by the Roland Morris Disability Questionnaire (RMDQ). Secondary outcomes were a change in pain intensity and health status. In addition, healthcare resource use was assessed. The data was collected

at baseline , three and six months after recruitment. The details of each section of the questionnaire are summarised below.

Baseline Characteristics

People were asked to provide their age, gender, ethnicity and marital status. The duration of CLBP and the use of medicines (both prescription and over the counter) and comorbidities at baseline were also recorded. Finally, the people needed to specify their highest educational qualifications and employment status.

The people were asked about their inabilities to perform their usual activities in the last six months due to CLBP; if they answered yes, the duration of this impairment needed to be specified. These topics were selected by the researcher as a result of reviewing previous studies and after discussion with the research team. These characteristics were chosen in order to compare our sample demographic data with relevant studies assessing similar interventions. The baseline questionnaire is in Appendix A.

- **Functional disability: Roland Morris Disability Questionnaire (RMDQ)** (152)

The questionnaire consists of 24 yes/no items related to physical functions associated with CLBP disability (152). The physical function domains include walking, bending over, sitting, lying down, dressing, sleeping, self-care and daily activities. The final score is the sum of positive answers, ranging from 0 (no disability) to 24 (most severe disability), where higher scores means greater disability.

- **Pain intensity: Brief Pain Inventory (BPI) - short form** (95)

The BPI was used to assess pain intensity and the impact of pain on daily function (95, 153). The BPI questionnaire contains 14 items, four items addressing pain intensity and seven items assess the interference. Each item is scored on a 0 to 10-point scale. The remaining items assess the pain medicines use and percent of pain relief from these medicines.

Pain intensity was measured as the mean of worst, least, average (in the last 24 hours) and pain right now. The pain interference is measured by calculating the mean of seven domains: general, mood, walking ability, work, relationship with others, sleep and enjoyment of life. The scores range from 0 to 10, where higher scores indicate more pain intensity and interference respectively.

In this measure, the people were asked to list their pain medicines in blank boxes and to determine the percentage of pain relief in the past 24 hours. This section was used to assess the medicines use over the study period.

- **Health status: Euroqol 5 Dimensions 3 Level instrument (EQ-5D-3L)** (87)

EQ-5D-3L is a standardised, generic instrument that assesses health-related quality of life (87). It consists of two parts: the first is the health status profile, consisting of five items to assess the five dimensions of mobility, personal care, daily activities, pain/discomfort and anxiety/depression.

Three states are defined for each dimension, from which the people have to choose the one that best reflects their situation. These three states describe absence of problems in that dimension (level 1), moderate problems (level 2) and serious problems (level 3).

The five dimensions of the EQ-5D descriptive system can give a total of 243 possible health states (or profiles) and each state is referred to using a 5-digit code. For example, the state 11111 indicates that there are no health problems in any dimension. The state 12123 indicates that there are no problems with mobility, some problems with self-care, none with usual activities, some problems with pain/discomfort and severe problems with anxiety/depression. Responses to the five dimensions can be converted into a single summary index using set values. In this study, the set values for the UK general population were used (154). The best health state possible (11111) is given a mean value of 1.00; therefore, the closer the mean value of the profile is to 1.00, the better the health state is.

The second part is a visual analogue scale (VAS) represented by a 20cm vertical line, graded from 0 (worst imaginable health state) to 100 (best imaginable health state). The patient is required to indicate on this scale the point that best represents his or her overall health on the day of the assessment.

The EQ VAS self-rating records the respondent's own assessment of their health status and are, therefore, not representative of the general population.

3.2.5.1 Reason for Selecting these Health Status Measures

The health status measures chosen for this study are supported by the recommendations of the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) group (77), an initiative to improve the design, conduct and reporting of clinical trials on pain.

The IMMPACT group recommends the use of a condition-specific measure to assess physical functioning in studies where a previously established and validated tool is available for that specific condition (77). The RMDQ is widely used in clinical trials for LBP; this is due to its good responsiveness and reliability compared with other measures (155). In addition, this tool is easily scored and interpreted. The BPI questionnaire measures the effect of pain on several domains, such as general activity and mood, which can be correlated with other measures to test the validity of the results. In addition, the validity and reliability of BPI have been documented in different settings and languages (77).

CLBP adversely affects the quality of life of patients. The IMMPACT group recommends the use of a generic quality of life measure (e.g. EQ5D) in studies assessing the effectiveness of an intervention in pain conditions (77). The use of this measure has been recommended as it allows a relevant comparison with other health conditions, which will be useful for cost-utility analyses.

Healthcare resource use

Healthcare resource utilisation over the six month study period was obtained using patient self-completed diaries to minimise the burden on people by reducing the length

and frequency of telephone calls. It also helped to reduce recall bias, as the people fill the diary prospectively. The diary includes five categories: general practitioner, nurse, other healthcare professional visits, PMS staff and contact with hospital. The other healthcare professionals include occupational therapists, physiotherapists, chiropractors, acupuncturists and pharmacists. The PMS visits include visits to pain consultants and senior physiotherapists. The secondary care visits were for MRI and facet joint injections or other back-related visits to hospital. These sections were colour coded; in each section, the patient should fill out the date and the reason for the contact. The people were asked to send the diaries back using Freepost envelopes, which were provided in their study pack.

The patient diaries used in this study had already been assessed for patient comprehension and acceptability in previous studies by our Patient and Public Involvement (PPI) collaborators and have been approved for use in previous studies in our department i.e. the New Medicine Service (NMS) (156).

3.2.6 Recruitment

The PMS staff gave their initial agreement to participate in the study after being approached by the chief investigator. A letter was sent to the pain consultant outlining information about the study and this was followed by meeting with clinical staff to answer questions about the study and to provide further information.

Two consultants and one advanced physiotherapist identified and invited eligible people to take part in the study. The PMS staff explained the study to the eligible participants. The researcher was not involved in participant identification and initial

approach. The pain consultants and physiotherapist accessed the participant identifiable data to assess their eligibility for the study.

If the participant expressed an initial interest in being involved in the study, the consultant provided the participant with a study information pack. The participant was encouraged to read the content of the study pack. Finally, the participant was asked by the PMS staff to provide his or her contact details to arrange a telephone call with the researcher within 24-72 hours, to allow the participant to consider their participation in the study.

In order to allow the research team to gather data at 24-72 hours post–baseline, the PMS administration staff provided the principal investigator with patient contact details using a secure NHS email account. The participant contact details were passed to the researcher using University of Nottingham secured email. The participant data was then entered into a password protected spreadsheet.

Within 24-72 hours of the initial participant consultation, the researcher contacted the participant to confirm their consent and to answer any questions related to the study. The participant was asked to answer questions related to his or her baseline function, pain and health status, along with demographic data. The participant was required to sign the consent form and send it back to the researcher by post. Each participant was also encouraged to record their healthcare resource use using the diaries. These diaries were returned by post at 3 months and at 6 months.

The researcher contacted the participant by phone to collect clinical outcome data after three and six months. To maximise the retention of the study's participants, each participant determined their preferred time for the researcher to contact him or her. If the patient did not respond to the first phone call, the researcher contacted the participant twice within one hour. The total number of calls was three, each 20 minutes apart. Another attempt was made on the following day in the case of no response. Furthermore, the participant was approached by letter to re-establish the contact. Participants who did not respond to phone calls after these attempts were presumed to have withdrawn from the study and no further contact was made.

3.2.7 Ethical Considerations

3.2.7.1 Ethical Approval

Ethical approval for the study was obtained from East Midlands - Nottingham 1 Research Ethics Committee in April 2015 (REC reference number 15/EM/0190). Subsequently, Research and Development (R&D) approval was granted from Nottinghamshire Healthcare NHS Foundation Trust in May 2015 (Appendix B). The researcher undertook good clinical practice training and informed consent for research training before R&D approval was granted.

3.2.7.2 Ethical Amendment

Due the slow recruitment rate, an amendment to the original study was suggested. Consequently, the Research Ethics Committee approved ethical amendment in

November 2015 (SA01 08-10-2015) and R&D approval was granted in the same month (Appendix C). The amendment to the ethical approval is described below.

3.2.7.3 Process of Obtaining Consent

Initially, the participant was required to send the consent form by post after confrming their participation in the study. However, it was noted that some people often forget to return the consent to the researcher. Therefore, it was suggested that the clinician should take consent from the participant during the visit and the reseacher should confirm it after 2-3 days.

3.2.7.4 Participant Payment

One possible cause of slow recruitment at the beginning of the study was that it started in the summer, when people are often away for holidays. Therefore, we thought that providing shop vouchers could improve participant recruitment and retention rate.

3.2.7.5 Study Period Extension

Due to the unexpectedly slow recruitment process, the study recruitment phase was extended until March 2016. Therefore, the last patient contact at the end of the study was on 30th August 2016.

3.2.7.6 Informed Consent

All participants provided written informed consent and the consent form was signed and dated by the participant before they entered the study (Appendix D). The consultant explained the details of the study and provided a Participant Information

Sheet with the study pack (Appendix E). The participant had sufficient time (1-3 working days) to consider their study participation. The researcher contacted the participant to confirm their consent and to answer any questions that the participant had regarding study participation. After signing the form, the participant was asked to return it to the research team by post, using the prepaid envelope. The reseacher then signed the consent form. One copy was sent back to the participant by post and the researcher kept the original form.

After the ethical amendment, the consent form was signed during the PMS visit and the participant was given two to three days to consider their participation. The researcher called the participant to confrm the consent and to answer any questions. If the candidate patient agreed to participate, the researcher signed the consent form and sent a copy to the participant.

3.2.8 Data Security and Participant Confidentiality

The data was entered into a password-protected spreadsheet. In addition, each participant was given a numeric code and this code was subsequently used in entering clinical outcomes and healthcare service use.

Participants' consent forms, questionnaires and diaries were kept in locked cabinets in the University of Nottingham and only the researcher had access to this data.

3.2.9 Data Management

The participant data was received from the PMS in the form of a spreadsheet, which contained the pack number, the patient's name, the NHS number, the date of visit,

contact number, preferred time slot and home address. This sheet was updated whenever new people were added.

An additional spreadsheet was created, which was also password protected, with the same participant details, to enable tracking of people and to keep a record of specific participant notes, such as the preferred method of filling the questionnaire, number of calls and reasons for declining, if possible. The dates for sending diary reminders and the three and six month questionnaires were also recorded in this spreadsheet to remind the researcher to send these documents at the right time.

The people reported their clinical outcomes and healthcare service use in paper format using questionnaires and diaries respectively. The data from the questionnaires was entered in Microsoft Excel 2010 (157) and analysed in STATA 11.1 (158).

3.2.10 Statistical Analysis

The data analysis was mainly descriptive and included the demographics of the study population, recruitment of participants and loss to follow-up. Simple descriptive statistics, mean and median, percentages and frequencies for categorical variables, were used to assess changes within health status measures (RMDQ, BPI and EQ-5D-3L) over the duration of the study. The Wilcoxon signed-rank test for continuous non-parametric data was used to assess the mean difference in health status measures.

In the presence of missing data, it is essential to recognise how much is missing and the pattern. The examining analyses include assessing proportions of people and time to loss of follow up, potential causes for loss of follow up and their characteristics

compared with participants who completed the study (159). This information is essential in understanding and interpreting the results.

For health status measures, three data sets were analysed. The first data set was for all study participants. The second data set was only for people who had completed the baseline, three months and six months (a complete case analysis). In the third data set, the missing data was handled using last observation carried forward (LOCF). For the purposes of this study, which achieved a sample size below its target, it was considered preferable to compare between the complete case analysis and LOCF set in order to identify similarities and differences in the pattern of change in clinical outcomes.

Both complete case analysis and LOCF have some limitations, especially if the data was missing not at random (MNAR), which means that specific patient-related factors were attributed to the missing data (160). An example of MNAR might be people with severe pain or depression, who are more likely to have missing data compared with people with a less severe status. Therefore, this was considered the best available option to account for missing data in this study, given that deriving an effect size is not applicable. As for medicines and healthcare resource use, two data sets were analysed, which include all people and a complete case analysis.

3.3 Results

3.3.1 Recruitment Process: Challenges and Changes

In total, 59 people were identified by pain consultants and received the study information pack. Among those identified, 32 people signed the consent form, 22

people did not respond to phone calls and 5 people declined to participate. Among those 32 people, 25 participants and 24 participants completed the three and six-month questionnaires respectively. As for the healthcare resource use diaries, 25 people completed the three-month diary, while 22 people returned the six-month diary. The recruitment flow is described in Figure 3-1.

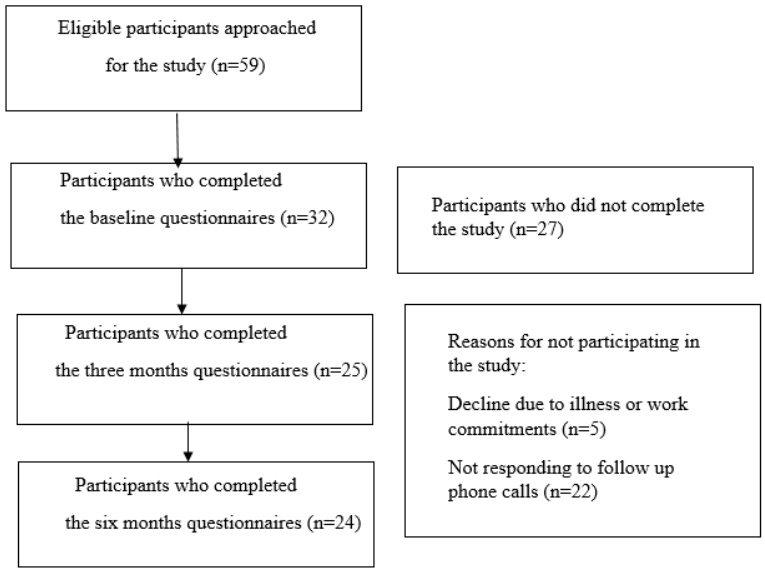


Figure 3-1 Recruitment flow

The study started at the beginning of June 2015, when study packs were sent to the PMS. The first participant was recruited one month later. The total number of people approached between June and August 2015 was 15, of which three participants declined participation and four people did not respond to phone calls.

After discussion with supervisors and PMS staff about the small number of recruited people and the non-respondents, this was attributed to the reduced number of

appointments during summer time as people are often away for holidays. Therefore, we were advised to wait until the school term started in the autumn and the full number of clinics was operating again. During September 2015, 11 people were approached; however, 7 people did not respond to subsequent telephone calls. We hypothesised that the summer season was still affecting participants' responses. This was clearly demonstrated in the following month as, in October, the number of non-respondents reduced and no people declined the participation.

Given the small number of people recruited in the early months of the recruitment period, we discussed the possibility of providing the people with an "inconvenience allowance".We had a discussion with a research ethics committee member about the type and amount of allowance that would be considered as being ethically appropriate. From this discussion, we concluded that a £10 voucher per questionnaire was reasonable. Therefore, each participant received £30 in vouchers if the three questionnaires were completed. After implementing these changes in the study, no people declined participation and all people who were invited to join the study after the amendments gave their consent at the PMS. However, five people did not return their baseline questionnaires despite their initial consent.

The number of people who were approached and who participated each month is summarised in Table 3-1.

Table 3-1 Number of participants approached and responses received during the 10 month recruitment period

Month	Approached	Participated	Declined	Did not respond
June 2015	0	0	0	0
July 2015	4	1	1	2
August 2015	11	7	2	2
September 2015	11	2	2	7
October 2015	9	7	0	2
November 2015	8	5	0	3
December 2015	4	2	0	2
January 2016	4	3	0	1
February 2016	5	3	0	2
March 2016	3	2	0	1
Total	59	32	5	22

3.3.2 Comparison between Respondents and Non-respondents

In order to understand the pattern of missing data, a comparison between people who completed all the questionnaires (complete responders), people who completed the baseline and three month questionnaires (partial responders) and people with baseline data only (non-responders) was undertaken. The difference between these three groups in terms of baseline characteristics is summarised in Table 3-2

Table 3-2 Comparison between responders and non-responders

Baseline characteristics	Complete responders	Partial responders	Non-responders
Mean RMDQ, (SD)*	12.5 (6.04)	15.6 (6.10)	16 (5.20)
Mean pain intensity, (SD)*	5.8 (1.30)	5.1 (1.80)	6.4 (2.60)
Mean pain interference, (SD)*	5.6 (1.80)	6.3 (0.35)	6.4 (2.20)
Mean age (years), (SD)	60 (13.80)	58.3 (27.50)	52.3 (11.30)
* Higher scores mean higher disability and pain			

From this comparison, it is clear that non-responders had high disability and pain intensity/interference compared with complete responders. In addition, the mean age of non-responders was lower than that of complete responders. A high baseline condition severity (161) and time commitment, especially in people of working age, are factors that affect patient participation in clinical trials (162, 163).

3.3.3 Baseline Characteristics

The total number of people recruited was 32. The mean age (range) was 58.8 (32-87), with an equal distribution of both genders. The mean duration of the CLBP is 12.7 years. The vast majority were white English and 62% had attained only CSE/GCSE/O levels. Among the participants included, 34.3% were retired, while 25% were in full-time employment. 43% of the participants had been unable to carry out their normal activities in the last six months due to CLBP. The characteristics of the participants included are illustrated in Table 3-3.

Table 3-3 Baseline characteristics of study participants

Sociodemographic variables (n=32)		
Mean age (range), years		58.8 (32-87)
Gender, female, n (%)		16 (50%)
Marital status, n (%)	Married/cohabiting	25 (78 %)
	Separated/divorced	5 (15%)
	Widowed	2 (6%)
Maximum education level attained, n (%)	CSE/GCSE/O level	21 (62%)
	A level	2 (6%)
	Degree	8 (25%)
	Other: Diploma	1 (3%)
Ethnicity, n (%)	White English	31 (96%)
	Other: white Slovak	1 (3%)
Work status, n (%)	Employed full time	8 (25%)
	Employed part time	2 (6%)
	Self employed	2 (6%)
	Unemployed	3 (9%)
	Unable to work due to long term sickness	3 (9%)
	Homemaker	3 (9%)
	Retired	11 (34%)
Unable to carry on work activities in the last 6 months, n (%)		14 (43%)
Monthly period of inability to carry on work activities, mean (range)		44.64 (0.25-288)
Duration of back pain (years), mean (range)		12.7 (0.25-62)
Current prescribed medicines, n (%)		Yes 24 (75%)
		No 8 (25%)
Current self-medicines, n (%)		Yes 11 (34%)
		No 21 (65%)

3.3.4 Comorbidities

In this cohort, 15 people did not report any comorbidity, 11 people reported one condition, four people had two conditions and two people had three conditions . The most frequent conditions were other musculoskeletal diseases, such as osteoarthritis, and respiratory conditions, such as asthma. Cardiovascular disease, including hypertension, was observed in this cohort.

Three people reported suffering from gastrointestinal problems, such as ulcerative colitis, with the same number reporting having hypothyroidism and diabetes. Two people were diagnosed with breast and prostate cancer. Psychiatric illnesses, such as depression, were not present as people with psychiatric conditions were excluded from the study. The type of comorbidity among the study participants is summarised in Table 3-4. The mean number of medicines per participant for comorbidities was 1.25 and ranged between 1 and 11 medicines.

Table 3-4 Type of comorbidity among study participants

Comorbidities	Frequency (%)
Musculoskeletal	6 (18%)
Respiratory	7 (21%)
Cardiovascular	5 (15%)
Gastrointestinal	3 (9%)
Metabolic	3 (9%)
Cancer	2 (6%)

3.3.5 Health Status Measures

Three trends of change in health status measures were observed over the follow up period, the first of which was improvement at six months. This trend of change was observed in the RMDQ and EQ5D-VAS component. The second trend was improvement at three months, followed by worsening at six months. However, the results at six months were still better than baseline. This was observed in the BPI-pain intensity and EQ5D-descriptive component. Finally, an improvement in the BPI-interference component was achieved at three months and the value remained the same at six months. At three months, the change in pain interference and EQ5D-descriptive scores was statistically significant, with the Pat 0.04 and 0.037 respectively.

The complete case analysis (n=24), imputed data (n=32) and full patient data (n=32, 25, 24 at baseline, three and six months respectively) show similar patterns of change in health status measures. The summary of these measures and the mean difference between baseline, three and six months data are presented in Table 3-5 and Table 3-6 respectively.

Table 3-5 Summary of health status measures over follow up period

Health status measure (mean, median, (range)	Full data			Complete case (n=24)			Imputed using LOCF (n=32)		
	Baseline n=32	3 months n=25	6 months n=24	Baseline	3 months	6 months	Baseline	3 months	6 months
RMDQ	13.5,13.5 (2-22)	11.9,13 (1-23)	11.1,9.5 (0-22)	12.5,12 (2-22)	11.5,12.5 (1-22)	11.1,9.5 (0-22)	13.5,13.5 (2-22)	12.8,13.5 (1-23)	12.5,13 (0-23)
BPI-intensity	5.9,6.1 (1-9)	5.2,5.5 (1-9)	5.5,6.1 (0-10)	5.8,5.8 (3-8)	5.2,5.5 (1-9)	5.5,6.1 (0-10)	5.9,6.1 (1-9)	5.5,5.6 (1-9)	5.6,6.3 (0-10)
BPI-interference	5.9,5.9 (1-10)	4.9,5.1 (0-9)	4.8,5.4 (0-10)	5.7,5.7 (1-9)	4.8,5.07 (0-9)*	4.8,5.4 (0-10)	5.9,5.9 (1-10)	5.2,5.6 (0-10)	5.2,5.7 (0-10)
EQ5D-descriptive	0.38,0.51 (-0.23-0.79)	0.50,0.62 (-0.07-1)	0.43,0.55 (-0.18-1)	0.4,0.62 (-0.23-0.79)	0.50,0.62 (-0.074-1)*	0.43,0.55 (-0.18-1)	0.38,0.51 (-0.23-0.79)	0.46,0.58 (-0.074-1)	0.40,0.51 (-0.18-1)
EQ5D-VAS	52,55 (15-90)	56,50 (20-100)	56,59 (0-100)	53,55 (15-90)	55,50 (20-100)	56,59 (0-100)	52,55 (15-90)	54,50 (20-100)	55,59 (0-100)

*using Wilcoxon rank test P<0.05 when compared to baseline

RMDQ = Roland Morris Disability Questionnaire, BPI = Brief Pain Inventory, EQ5D descriptive = Euroqol 5 dimensions, EQ5D VAS = Euroqol 5 dimensions Visual analogue scale

Table 3-6 The mean difference between baseline, three and six month data

Mean difference, (SD)	Full data		Complete case (n=24)		Imputed using LOCF (n=32)	
	Three months n=25	Six months n=24	Three months	Six months	Three months	Six months
RMDQ	-1.6 (1.60)	-2.4 (1.70)	-1.04 (2.70)	-1.4 (5.10)	-0.7 (2.40)	-1 (4.50)
BPI-intensity	-0.7 (0.55)	-0.46 (0.62)	-0.54 (1.80)	-0.30 (2)	-0.46 (1.50)	-0.28 (1.80)
BPI-interference	-0.98 (0.60)	-1.1 (0.66)	-0.88 (1.90)	-0.91 (2.30)	-0.64 (1.70)	-0.66 (2.09)
EQ5D- descriptive	0.11 (0.09)	0.04 (0.98)	0.10 (0.24)	0.03 (0.25)	0.07 (0.21)	0.02 (0.22)
EQ5D- VAS	3.7 (6.30)	4.3 (6.50)	2.1 (21.40)	3.29 (21.80)	1.9 (18.50)	2.7 (18.90)
RMDQ = Roland Morris Disability Questionnaire, BPI = Brief Pain Inventory, EQ5D descriptive = Euroqol 5 dimensions, EQ5D VAS = Euroqol 5 dimensions Visual analogue scale						

3.3.5.1 Achieving minimal clinically important difference (MCID) in health status measures

The imputed data set was analysed using LOCF in order to determine the proportion of people achieving the MCID in the health status measures.

3.3.5.1.1 MCID in functional disability

The people were categorised based on their RMD scores. If the mean difference was more than a 2.5 point reduction compared with baseline, this is categorised as substantial improvement (155). If the patient had a reduced RMDS score but did not achieve MCID, they were categorised as "improved", which means that the improvement was less than 2.5, "unchanged" if the score remained the same, or "deteriorated" if the score at follow-up was higher than baseline. The distribution of people according to their change in functional disability is presented in Figure 3-2.

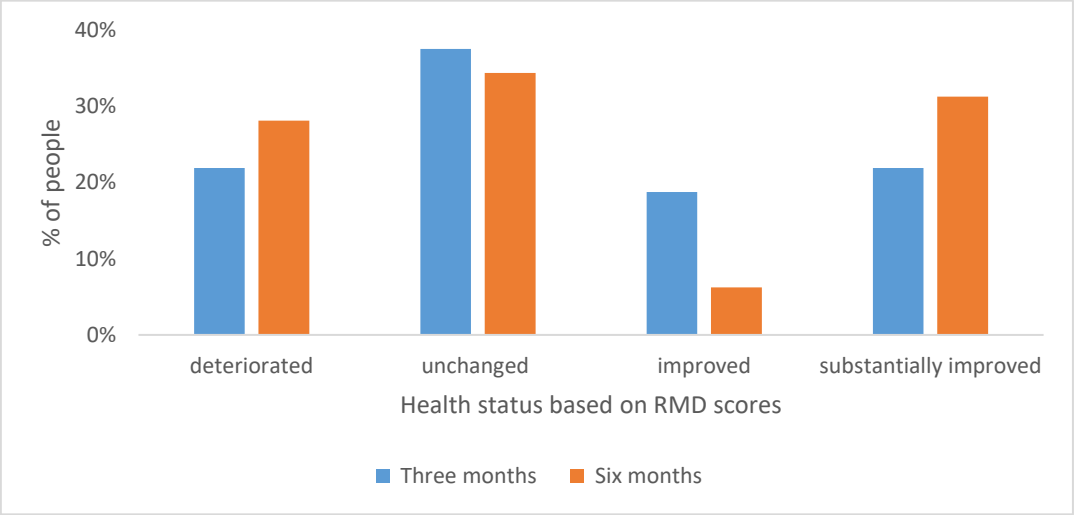


Figure 3-2 Stratification of people based on MCID in functional disability using RMDS over the follow up period (n=32)

3.3.5.1.2 MCID in pain intensity

Reductions of ≥30% appear to reflect at least moderate clinically important differences and reductions in chronic pain intensity of ≥50% appear to reflect substantial improvements (164). People reporting less than 10% improvement were categorised as having "no meaningful change", "unchanged" if the score remained the same, or "deteriorated" if the score at follow up was higher than baseline. The distribution of people according to their change in pain intensity level is presented in Figure 3-3.

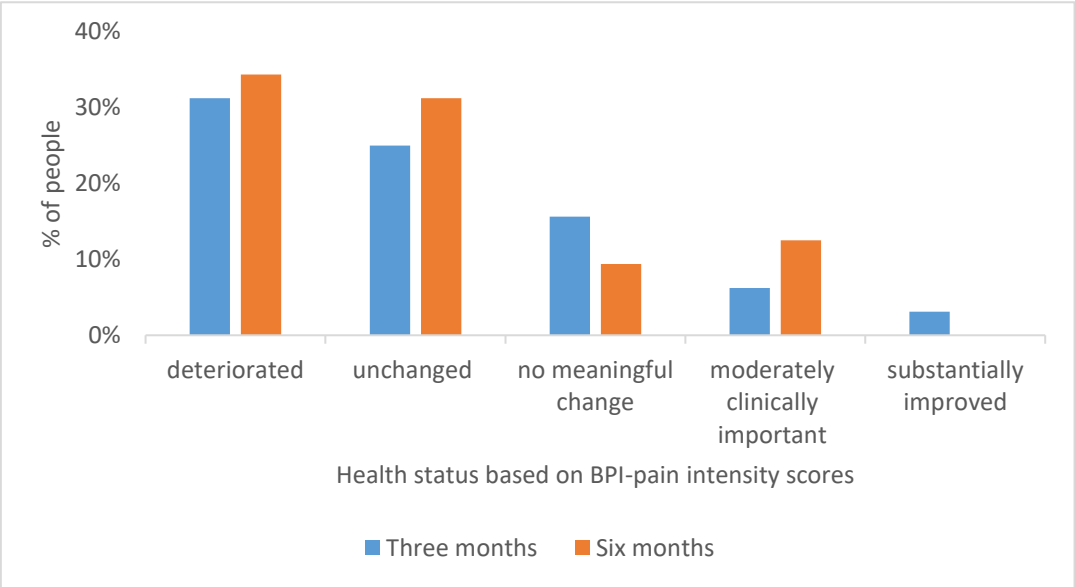


Figure 3-3 Stratification of people based on pain intensity score over the follow up period (n=32)

3.3.5.1.3 MCID in pain interference

As with pain intensity, people were classified into groups according to the recommendations of the IMMPACT group on standards for interpreting clinically important changes for pain interference (164). A reduction of one point in the overall interference of pain is considered as minimally clinically important. However, unlike pain intensity, the criteria for defining moderate and substantial changes have not been described by the IMMPACT group (164).

People not meeting the criteria for the MCID were either classified into “no clinically important reduction” if the reduction in the overall interference score was less than one point, or into “deterioration” if the overall interference score was higher at six months compared to the baseline. The distribution of people according to their change in pain interference level is presented in Figure 3-4.

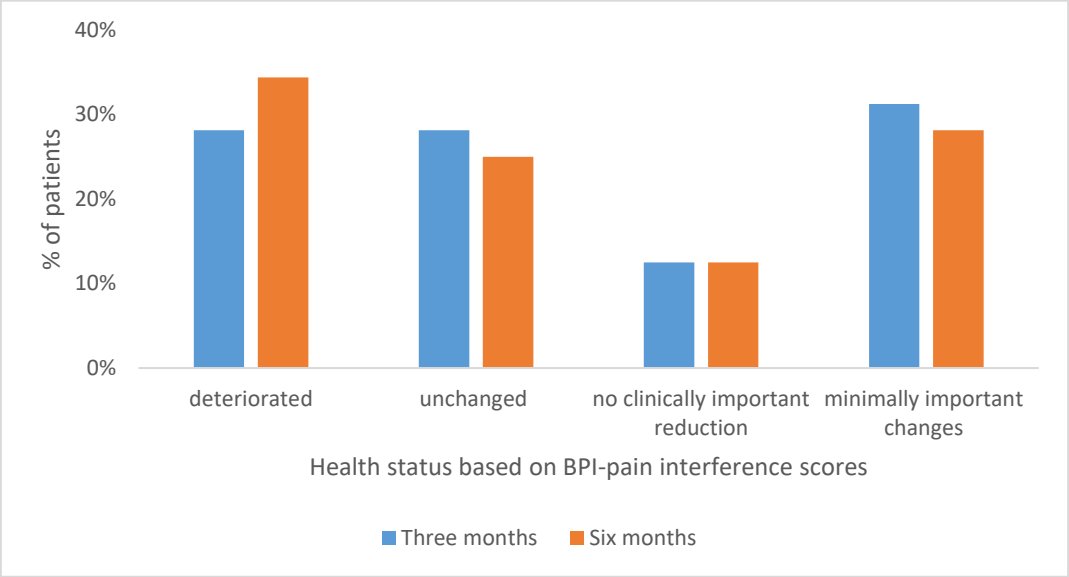


Figure 3-4 Stratification of people based on pain interference score over the follow up period (n=32)

Regarding achievement of the MCID, the largest improvement was observed in pain interference, with 10 (31%) and 9 (28%) people having achieved the minimum important change over three and six months respectively. This was followed by improvement in functional disability using RMDS, with 7(21%) and 10 (31%) people having achieved a substantial improvement over three and six months respectively. Finally, only one patient achieved a 50% reduction in pain intensity, which is considered to be a substantial improvement. 2 (6%) and 4 (12%) people achieved a moderate reduction in pain intensity over three and six months respectively.

3.3.6 Medicines Use

The participants used several analgaesic medicines during the study period. Prescription medicines included opioids, opioid/paracetamol combinations,

antidepressants/anticonvulsants, non-steroidal anti-inflammatory drugs (NSAIDS) and topical medicines. A list of all medicines is provided in Table 3-7.

Table 3-7 Common medicines used by study participants

Medicines class	Medicines name
Opioid	Morphine
	Codeine
	Tramadol
	Oxycodone
	Dihydrocodeine
	Buprenorphine
Opioid/paracetamol combination	Co-codamol (paracetamol and codeine)
	Co-dydramol (dihydrocodeine tartrate and paracetamol)
NSAIDs	diclofenac
	naproxen
	ibuprofen
Paracetamol	-
Antidepressants/anticonvulsants	gabapentin
	amitriptyline
	trazadone
	sertraline
	pregabalin
	duloxetine
Other	Nefopam
Topical medicines	Algesal cream (diethylamine salicylate), capsaicin cream

Among the study participants, 24 people reported using prescription medicines while 11 people were using over the counter (OTC) medicines. Six people used both prescription and OTC medicines.

The mean number of medicines used per patient did not change over the follow up period (1.5 medicines per patient). However, several findings were observed. Firstly, the use of morphine, codeine and oxycodone was discontinued. Nonetheless, the use of tramadol increased over the six month study period. Secondly, the mean NSAIDs use per patient was reduced at six months, with the main reduction being in naproxen and ibuprofen. Thirdly, the mean use of antidepressant/anticonvulsant increased at six months. The use of gabapentin increased over the follow up period. Duloxetine and sertraline were introduced at six and three months respectively. However, amitriptyline, trazadone and pregabalin were discontinued.

The medicines use over the follow up period is presented in Table **3-8** and Table **3-9**.

Table 3-8 Mean medicines use per patient stratified by medicines class over the follow up period

Mean medicines use per patient (range)	Full cohort			Complete case (n=24)		
	Baseline n=32	Three months n=25	Six months n=24	Baseline	Three months	Six months
Paracetamol	0.28 (0-1)	0.36 (0-1)	0.29 (0-1)	0.25 (0-1)	0.37 (0-1)	0.29 (0-1)
Opioids	0.37 (0-2)	0.44 (0-1)	0.41 (0-1)	0.29 (0-1)	0.41 (0-1)	0.41 (0-1)
Opioid-paracetamol combinations	0.21 (0-1)	0.16 (0-1)	0.20 (0-1)	0.25 (0-1)	0.12 (0-1)	0.20 (0-1)
NSAIDs	0.46 (0-2)	0.32 (0-2)	0.25 (0-1)	0.41 (0-2)	0.25 (0-1)	0.25 (0-1)
Antidepressant/anticonvulsant	0.21 (0-1)	0.24 (0-1)	0.25 (0-2)	0.25 (0-1)	0.25 (0-1)	0.25 (0-2)
Nefopam	0.31 (0-1)	0.04 (0-1)	0.04 (0-1)	0	0.04 (0-1)	0.04 (0-1)
Topical analgaesic	0.03 (0-1)	0.08 (0-1)	0.04 (0-1)	0.04 (0-1)	0.08 (0-1)	0.04 (0-1)

Table 3-9 Mean medicines use per patient stratified by medicines item over the follow up period

Mean medicines use per patient	Full cohort			Complete case (n=24)		
	Baseline	Three months	Six months	Baseline	Three months	Six months
Tramadol	0.15	0.32	0.29	0.12	0.29	0.29
Morphine	0.06	0	0	0.04	0	0
Codeine	0.03	0	0	0	0	0
Oxycodone	0.03	0	0	0	0	0
Dihydrocodeine	0.06	0.08	0.08	0.08	0.08	0.08
Buprenorphine	0.03	0.04	0.04	0.04	0.04	0.04
Paracetamol/codeine combination	0.18	0.12	0.16	0.20	0.12	0.16
Paracetamol/dihydrocodeine combination	0.03	0.04	0.04	0.04	0.04	0.04
Ibuprofen	0.25	0.16	0.16	0.25	0.12	0.16
Diclofenac	0.03	0.08	0.04	0.04	0.08	0.04
Naproxen	0.18	0.08	0.04	0.12	0.04	0.04
Gabapentin	0.12	0.12	0.16	0.12	0.12	0.16
Amitriptyline	0.06	0.04	0	0.08	0.04	0
Trazadone	0.03	0	0	0.04	0	0
Sertraline	0	0.04	0.04	0	0.04	0.04
Pregabalin	0	0.04	0	0	0.04	0
Duloxetine	0	0	0.04	0	0	0.04

Over the study period, a combination of two medicines was the most observed (9 people at baseline and three months and 11 people at six months). At baseline, 7 people were not on any medicines while one patient was on four medicines. At the end of the follow up, 5 people were not on any medicines and no people received more than three medicines. The medicines combination over the follow up period is presented in Table **3-10**

Table 3-10 Use of medicines combination over the follow up period

Time point (n, %)	Full cohort (n =32)					Complete case (n=24)				
	Number of medicines					Number of medicines				
	None	One	Two	Three	Four	None	One	Two	Three	Four
Baseline	7 (21%)	5 (15%)	14 (43%)	5 (15%)	1 (3%)	6 (25%)	5 (20%)	9 (37%)	3 (12%)	1 (4%)
Three months	5 (20%)	5 (20%)	9 (36%)	6 (24%)	0	5 (20%)	5 (20%)	9 (37%)	5 (20%)	0
Six months	5 (20%)	5 (20%)	11 (45%)	3 (12%)	0	5 (20%)	5 (20%)	11 (45%)	3 (12%)	0

3.3.7 Healthcare Resource Use

The mean health visits per patient was 4 and 2.9 visits at the end of three and six months respectively. The reduction was mainly in GP, nurses, physiotherapists, PMS, MRI and facet injections. However, there were increases in occupational therapy, acupuncture and hospital physiotherapy visits. The mean healthcare resource use stratified by type of visits over the follow up is presented in Table **3-11** and Table **3-12**.

Table 3-11 Mean healthcare resource use per patient stratified by type of visits over the follow up

Mean healthcare resource use per patient (range)	Full cohort (n=32)		Complete case (n=22)	
	1-3 months (n=25)	4-6 months (n=22)	1-3 months	4-6 months
General practitioner (face to face encounters)	1.04 (0-4)	0.59 (0-4)	1.09 (0-4)	0.59 (0-4)
Nurse	0.12 (0-3)	0	0.13 (0-3)	0
Physiotherapist at primary care	0.84 (0-5)	0.86 (0-6)	0.90 (0-5)	0.86 (0-6)
Other healthcare professional*	0.76 (0-5)	1.04 (0-5)	0.68 (0-5)	1.04 (0-5)
PMS**	0.68 (0-3)	0.27 (0-2)	0.68 (0-3)	0.27 (0-2)
MRI	0.32 (0-1)	0	0.31 (0-1)	0
Facet joint injection	0.16 (0-1)	0.04 (0-1)	0.13 (0-1)	0.04 (0-1)
Physiotherapist at secondary care	0.08 (0-2)	0.13 (0-3)	0.09 (0-2)	0.13 (0-3)
*PMS= pain management service, Including: occupational therapist, acupuncturist, chiropractor and pharmacists. **including pain consultant and advanced physiotherapist.				

Table 3-12 Disaggregated mean healthcare resource use per patient stratified by type of visits over the follow up

Mean healthcare resource use per patient (range)	Full cohort		Complete case (n=22)	
	1-3 months (n=25)	4-6 months (n=22)	1-3 months	4-6 months
Occupational therapist	0.20 (0-4)	0.09 (0-2)	0.04 (0-1)	0.09 (0-2)
Chiropractor	0.08 (0-2)	0.04 (0-1)	0.09 (0-2)	0.04 (0-1)
Acupuncturist	0.2 (0-5)	0.59 (0-5)	0.22 (0-5)	0.59 (0-6)
Pharmacist	0.28 (0-3)	0.31 (0-4)	0.31 (0-3)	0.31 (0-4)
PMS - pain consultant	0.44 (0-2)	0.22 (0-2)	0.40 (0-2)	0.22 (0-2)
PMS - physiotherapist	0.24 (0-1)	0.04 (0-1)	0.27 (0-2)	0.04 (0-1)

3.4 Discussion

There were four main findings from the study. Firstly, despite the initial recruitment problems it was possible to recruit and retain people to the study. Secondly, using the health status measures had a high completion rate. Thirdly, clinical outcomes were improved at three months. Finally, it was feasible to collect healthcare resource use data.

3.4.1 Feasibility of Recruitment and Retention

Recruitment in health services research can be challenging (165). In addition, difficulties in recruiting people in chronic pain studies have been documented previously (166). A possible reason for inadequate recruitment in pain research is that the emotional distress associated with pain reduces the motivation to participate in studies (167). Therefore, several strategies have been proposed in the literature to improve the recruitment and retention of participants. These strategies can range from simple reminders and reducing the length of measurement tools to providing incentives to study participants (168, 169). However, evidence on the best strategy that should be

implemented is limited by the number and quality of studies. Bower et al. suggested that the principal investigator should rely on previous experience and subjective judgment (165). One of the key factors that is considered to improve recruitment is the healthcare professionals' attitudes towards the research. In this study, the pain consultant at the PMS and the lead of the Clinical Commissioning Group were highly motivated and facilitated the process of understanding the workflow of the PMS. Several meetings were held to discuss the practical issues that might be encountered during the study.

The PMS staff members were responsive to all queries and were cooperative in maintaining the process of recruitment. In addition, the researcher maintained regular contact with the administration staff and the pain consultant throughout the study recruitment. It has been found that regular communication throughout the recruitment period, in addition to regular study updates and reminders, is considered to be a useful method of enhancing participant recruitment (170). Furthermore, other factors that might significantly affect the recruitment were considered, such as the convenience of participant contact, in terms of time and method of providing information, and the selection of outcome measures during the study's design.

Once the people were invited to take part in the study, they had the opportunity to select their preferred time during which the researcher could call. Moreover, if the participant expressed a preference for sending the documents by post instead of completing the questionnaire over the phone, Freepost envelopes were provided in their study information pack. Finally, the time required to complete the questionnaire ranged from 10 to 15 minutes, which could be considered as appropriate (168).

Another issue that needed to be addressed as part of the recruitment challenges was the process of gaining consent. In this study, the participants who showed interest in taking part in the study had to return the consent form using the Freepost envelope provided. However, some consent forms were not returned. In an effort to reduce the burden on participants, we suggested that the consent should be taken from the participant at their visit and then reconfirmed by the researcher after two to three days. This was discussed with the service staff members and they were willing to take the consent from each participant and send them back to us using Freepost envelopes. Finally, the exclusion critiera in this study, which were described in section 3.2.4, might also lead to a small sample size, as people with acute LBP and other causes of back pain were not eligible.

In this study, pain consultants in the PMS were responsible for identfying and recruiting eligible particiants. This might cause selection bias as the pain consultants might approach people who are likely to respond to postal questionnaires and have the ability to complete healthcare resource diaries and, therefore, people with less ability to be involved in the study might be not approached. In future studies, the researcher should recruit eligible participants to reduce selection bias, thus ensuring that the sample is representitve of the service users.

Despite all the efforts to improve recruitment, the sample size was small and there were several possible reasons for this. Firstly, the pain consultant might not have had the time to recruit participants, due to a busy practice with little time to make recruitment a priority. In addition, the lack of financial incentive for the pain consultants might also have affected the recruitment (171). Secondly, participant-related factors, including time commitment (172, 173), illness severity (161) and old

age (161, 162), might also affect the recruitment rate as those individuals might have limited mobility and lack motivation to participate in pain trials (167). Finally, seasonal variations have been documented as one of the possible causes for low recruitment (174). However, the data from this study is insufficient to support these assumptions as data was not collected on the reasons for declining participation or not responding to follow up contacts, as this was considered an additional burden on the participants. Therefore, limited conclusions can be drawn on factors affecting recruitment.

In this study, the dropout rates were 21% and 25% over three and six months respectively. The reasons for this are unknown; however, from this study, younger people and those who had a higher level of pain and disability at baseline were not retained. In a similar study conducted by Sephton et al., the dropout rate was 21% and 31% over three and twelve months respectively (175). In addition, similar trends of loss of follow-up were observed (175). People who did not complete the follow-up data tended to be younger and employed, with the mean age of non-responder being 50.5 years compared with responders, whose mean age was 57.8 years. The dropout rate and the trend of loss of follow up reported by Sephton et al. was consistent with our data. This indicates that greater efforts would be needed to retain participants with work commitments and those having higher disability and pain. Greater attention needs to be paid to agreeing an acceptable method and frequency of communication with participants who have work commitments. For people with severe pain, it might be better to collect the data over the phone or via face to face interviews at the service to minimise the burden of filling out the questionnaire and sending it by post.

3.4.2 Feasibility of Data Collection Tools

In this study, the RMDQ, the BPI and the EQ5D-3L had high completion rate at all time points. The estimated time to complete these questionnaires was less than 15 minutes, which might have enhanced the completion rate. This is consistent with the findings reported by Pincus et al. in assessing the feasibility of completing health status measures, including those used in our study (176). Furthermore, people were able to complete the diaries and return them in the post. This suggests that the selected measures and tools were acceptable to people for studies with a follow up period of up to six months. However, for studies with a longer follow up, health status measures and resource utilisation need to be collected on regular basis using an electronic patient reported outcome measures system.

A study was recently conducted in the UK in order to assess the feasibility of collecting patient reported outcomes (PROs) for people with musculoskeletal conditions managed by chiropractors (177). This study aimed to assess a web-based patient reported outcome measures (PROMS) system that collects data on health outcomes in addition to cost of care. The study found that routine collection of outcomes was feasible and can be achieved using a web-based system. Implementing this type of system nationally might serve as an important research tool as implementing such a system might ensure the completeness of patients' data, in addition to reducing the time and staff needed to collect the data.

3.4.3 Potential Clinical Effectiveness

From this cohort, several findings were observed. Firstly, functional disability improved at six months. Pain interference improved at three months and the effect was maintained until the end of follow-up, while the effect on pain intensity was not maintained but was still better than baseline.Substantial improvement in terms of

achieving MCID was observed in pain interference, followed by functional disability; the least improvement was observed in changes in pain intensity level. As for healthcare resource use, visits to primary care, PMS and secondary care were also reduced between four and six months, compared with the initial three month study period. Moderate changes in disability and pain can be attributed to the conservative pattern of prescribing prescription medicines, as only 25% of people were not given any medicines at baseline.

In the UK, several cohort studies (175, 178-180) have been undertaken to assess the effectiveness of these services in terms of clinical outcomes, changes in referral patterns and healthcare resource use. Sephton et al. conducted a cohort study to assess the effectiveness of a physiotherapist-led service for people with musculoskeletal conditions (175). The outcome measures were health status questionnaires, using EQ5D and pain intensity using the visual analogue scale. The results showed small but significant improvements in EQ5D and pain intensity. The mean changes from baseline in the EQ5D (0-1) at three and 12 months were 0.044 (95%CI 0.001-0.086) and 0.04 (95%CI 0.003-0.093), respectively, while the mean changes from baseline in pain intensity (0-10) at three and 12 months were -0.72 (95%CI -1.15 to -0.29) and -0.80 (95%CI -1.31 to -0.29) respectively.

Another UK-based study was conducted to evaluate clinical services at primary-secondary care interface (179, 180). This was a prospective cohort study with a sample size of 2166 participants. The outcome measures were the Short Form Health Survey (SF-36) and hospital anxiety and depression (HAD). The mean age was 51 years and 57% were females; among these participants, 53% were employed and 45% had time off work due to musculoskeletal problems. As for clinical outcomes, a small but

significant mean improvement was observed in SF-physical functioning and pain domains at 12 months, with the mean change being 1.82 (95%CI 1.24 to 2.39) and 4.19 (95%CI 3.55 to 4.83) respectively. The sample characteristics in this study were similar to the cohort in this study with regards to mean age and gender mix and the change in clinical outcomes was also consistent with our findings. However, it was not possible to compare healthcare resource use between both studies because only factors affecting the resource utilisation were reported, not the mean use of primary care and other healthcare services.

Roddy et al. (180) reported that people with a high level of pain interference at baseline have more visits to primary care and PMS after having the intervention, compared with people with less severe pain. The adjusted relative risk (RR) was 2.26 (95%CI 1.25 to 4.09). In addition, people with CLBP reported higher use of healthcare services compared with people with other musculoskeletal conditions, with the adjusted RR being 2.17 (95%CI 1.06 to 4.47).

Therefore, people with high pain interference at baseline and CLBP require special attention as they are considered greater utilisers of healthcare resources. This can be performed by targeting risk factors in those people that lead to poor outcomes, including baseline physical functioning and pain intensity. Some limitations in these cohorts have been identified (175, 180); the lack of a well-defined comparator group might lead to inaccurate estimation of the actual effect of the service, which affects the internal validity of the study. Regarding external validity, the people were recruited from one study site and, hence, this limited the generalisability of study findings.

The aim of this PhD is to evaluate the cost-effectiveness of PMS through a service evaluation study. Due to the small sample size and a lack of comparative group in this

study, mean age and initial distribution of pain intensity level were combined with other published estimates in Chapter 5 in order to populate the decision analysis model and to perform an indicative economic evaluation of PMS compared with SC for people with CLBP. These estimates were selected to reflect the characteristics of people attending PMS in Nottingham. Further details are discussed in Chapter 5.

3.4.4 Strengths and Limitations

This study looked at both clinical outcomes and healthcare resource use for people attending a PMS. As for the clinical outcomes, the use of three measures that address back pain-related disability, pain intensity and interference and a generic health utility measure help to investigate CLBP from several domains, as CLBP results from an interaction between physical and psychosocial components. In addition, this study provides comprehensive data about the type and trend of medicines and healthcare resource use among people with CLBP attending this service.

Furthermore, the choice of study design was based on the MRC recommendation for evaluating complex interventions (150). The MRC recommends evaluating the intervention through observational and developmental work, followed by an exploratory trial, before conducting the definitive evaluation. This is required to identify key uncertainties in the design and assessment of the PMS and its evaluation. Finally, this study highlights the challenges in recruitment processes in health services research for people with CLBP, which could be useful for future studies.

However, this study has some limitations; the lack of a comparator group and the small sample size at baseline, and then the loss of follow up at three and six months, did not allow use of any inferential statistics because the study was not powered to detect any statistical difference. In this study, the definition of standard care for CLBP varies

considerably across different settings and clinical contexts. Moreover, given that this study was not funded, it was not feasible to recruit people as a comparator from different settings. In addition, this study recruited people from one setting only; therefore, the sample might not be representative of people with CLBP attending PMS.

3.5 Conclusion

Community-based PMS have the potential to improve functional disability and pain interference for people with CLBP in the primary care setting by providing well-timed access to a specialised pain management team, ensuring effective use of pain medicines and reducing healthcare resource use. However, these results must be interpreted with caution because of the lack of a comparator group, which did not allow for a direct comparison with people managed in the SC setting. In addition, the study participants were recruited from a single geographical region, which limits the generalisability of our results.

Chapter 4

Cost-Effectiveness of Pain Management Services (PMS) for Chronic Low Back Pain: A Systematic Review of Published Studies

4.1 Introduction

Given the increasing prevalence of CLBP (181) and the moderate effect size and high cost of PMS (16), there is a need to critically appraise the cost-effectiveness of these services in order to support stakeholders and decision makers in the commissioning and reimbursement of PMS.

Therefore, the aim of this systematic review is to summarise and critically appraise the current evidence for the cost effectiveness of PMS in managing CLBP.

The objectives include:

1. To retrieve studies evaluating the cost effectiveness of PMS compared with standard care for people with CLBP.

2. To summarise and critique the key elements of the retrieved economic evaluations, including:

- Study design
- Health status measures and healthcare resource use data
- Type of sensitivity analysis
- Main economic evaluation results.

3. To inform the development of an indicative economic evaluation presented in Chapter 5.

4.2 Methods

4.2.1 Types of studies

Full economic evaluations (i.e. cost effectiveness, cost minimisation, cost-benefit analysis, cost utility and cost consequences), undertaken from any perspective and conducted alongside RCTs or based on decision analysis models, were included in this review.

Published protocols, conference papers and observational studies, such as cohort, case control and non-randomised studies, were excluded. Partial economic evaluation studies were also excluded, as these types of studies either report costs (financial evaluation), or outcomes (clinical evaluation), or costs and outcomes of one intervention only (descriptive rather than evaluative study). This is a basic criterion for the definition of an economic evaluation (182).

4.2.2 Types of participants

Adults (age >17 years) who had been referred to PMS with CLBP were included. The Cochrane Back Review Group (CBRG) does not recommend mixing studies about acute and chronic low back pain as the underlying causes for both conditions differ to a greater or lesser extent and, therefore, their response to the intervention might be systematically different (183). Therefore, people with acute or sub-acute low back pain lasting for less than three months were excluded. People with low back pain caused by cancer, infection, cauda equina syndrome or inflammatory disorders, such as spondylitis, were excluded, as these types of people require intensive and urgent medical consultations not easily managed by primary care.

4.2.3 Types of interventions

Although PMS have been recommended in clinical practice guidelines, there is still no consensus around the exact definition of these services (184). Based on the systematic review by Kamper et al. (15), PMS are defined as health services targeting at least two of the social, physical, psychological and/or occupational aspects provided by one or more healthcare professionals. Given the wide range of terms used to describe these services, we included all relevant terms in our search strategy. The terms including multidisciplinary, interdisciplinary, multimodal, multiprofessional, pain clinics and rehabilitation clinic. An inclusive strategy was adopted in order to identify all relevant publications and then a detailed assessment of the service was undertaken.

PMS based in primary and secondary care were eligible. The components of the services could include pharmacological treatments, physiotherapy, cognitive behavioural therapy, complementary medical approaches, such as acupuncture, and other relevant specialties, including occupational therapy and social services. PMS that offered fewer than two types of treatment modalities within the service were excluded.

4.2.4 Types of outcome measures

PMS can aim to either improve functional disability and pain or focus on the vocational outcomes, such as return to work. Therefore, the complex multidimensional aims of these services require the measurement of a variety of outcomes that best address the study aims and research questions. Patient-reported outcomes, such as pain intensity, functional disability, quality of life and return to work, were assessed. Healthcare resource utilisation, which includes direct medical costs was also examined.

4.2.5 Search methods for study identification

Electronic searches were conducted in MEDLINE, EMBASE and PsycINFO from their inception to August 2017. The NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment Database (HTA) in the Centre for Reviews and Dissemination (CRD) were also searched. Reference lists were checked to identify relevant publications.

CBRG search terms for "back pain" were used in the search strategy (185). For search terms related to health economics, the Scottish Intercollegiate Guidelines Network (SIGN) search filters were accessed to identify relevant terms (186). Furthermore, to search for "multidisciplinary", similar systematic reviews were explored for their keywords (15, 187). Finally, the search was restricted to studies about humans and published in English. The terms used in the search strategy are listed in Appendix F. The systematic review protocol have not been registered in the PROSPERO database; however, the abstracts have been published at a well-known health economics conference (188).

4.2.6 Methodological quality assessment

For RCTs, the 12 item checklist recommended by the CBRG assessed the risk of bias (183, 185). This tool addresses several domains related to a study's internal validity. According to the CBRG guidelines (183, 185), a study is considered to have a "low risk of bias" if at least six domains were categorised as having a low risk of bias.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was used to assess the methodological quality of reporting economic studies (189). The CHEERS items are listed in Appendix G.

Two reviewers screened the titles and abstracts and then one reviewer extracted the data from the eligible studies. The kappa statistic that measures the interrater reliability has not been performed; however, a third reviewer resolved disagreements if necessary.

The extracted data from each study contained author name, country, year, participant characteristics, intervention, comparator and outcomes. Data allowing assessment of risk of bias and adherence to CHEERS quality criteria were also extracted.

4.3 Results

The initial search retrieved 2,744 publications. After removing duplicates, the number of results was 2,208. When these results were limited to ‘English’ and ‘human’, the results numbered 2,019. Of the 2,019 results, 1,997 were assessed via the title and abstract by two reviewers as not relevant to the scope of this systematic review. The flow chart diagram of the included studies and the reason for studies having been excluded is presented in Figure 4-1 .

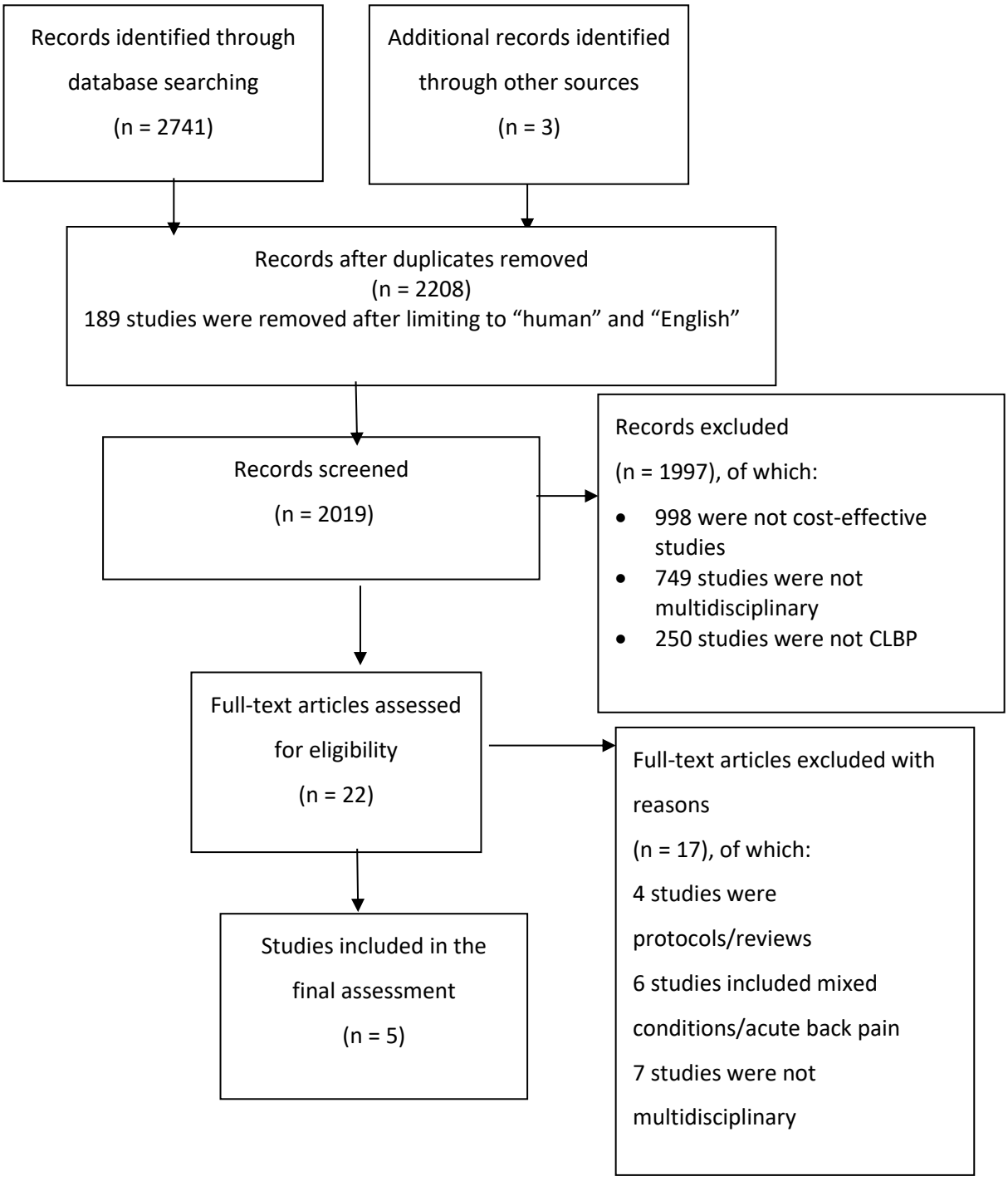


Figure 4-1 Flow Chart Diagram

The remaining 22 full text articles were assessed for eligibility. Only five studies fulfilled our inclusion criteria. Seventeen studies were excluded and details of the excluded studies and the reasons for exclusion are described in Appendix H.

4.3.1 Study characteristics

Five studies were included in the review; two studies were conducted in Norway (22, 26), two in the Netherlands (20, 25) and one in the UK (21). These studies were published between 2002 and 2014. The characteristics of the included studies are summarised in Table 4-1. The total number of participants in the five studies was 1,023, with the sample size ranging from 134 to 349. Two of the studies only included adults in employment taking sick leave due to CLBP (20, 26). The mean age of the participants ranged from 41 to 45.5 years, with a similar distribution of males and females. The mean duration of CLBP ranged between 5 and 8 years.

Table 4-1 Characteristics of the included studies

Study ID	Setting	Target population/Sample size	Intervention	Comparators
Skouen 2002 (26) Norway	Outpatient spine clinic	Patient sick listed for at least 8 weeks or employees not on sick leave but sick listed for at least 2 months /year n=195	Light multidisciplinary programme (assessment by physiotherapist and psychologist + individual education and feedback) Extensive multidisciplinary programme (4-week programme - 6 hr session 5 days/week) consisting of CBT, education, exercises, work place intervention)	Usual care
Rivero-Arias 2005 (21) United Kingdom	Secondary care	18-55 years with CLBP > 1 year n=349	Intensive rehabilitation programme (education + exercise) led by a physiotherapist and clinical psychologist	Spinal stabilisation surgery
Smeet 2009 (25) Netherlands	Primary care	Age between 18-65 with CLBP>3 months with RMD score >3 n=172	Active physical treatment + graded activity + problem training	2 comparators: active physical treatment and graded activity plus problem training
Lambeek 2010 (20) Netherlands	Primary and secondary care	Adults (18-65) with CLBP in paid work for at least 8 hr/week on partial sick leave n=134	Integrated care programme (workplace intervention + graded activity)	Usual care
Johnsen 2014 (22) Norway	Hospital	Adults with CLBP > 1 year with degenerative change in lumbosacral intervertebral disc n=173	Multidisciplinary rehabilitation (outpatient programme focussed on exercise and CBT delivered by a physiotherapist and physical medicine specialist)	Total disc replacement surgery
CLBP = chronic low back pain, CBT = cognitive behavioural therapy, RMD = Roland Morris Disability.				

A wide range of outcome measures were used in the studies included in this review. Return-to-work (RTW) was the primary outcome in three studies (20, 21, 26). Four studies used two measures for disability (21, 22, 25, 190). Regarding the baseline measures of disease severity, the mean score of functional disability using the Roland Morris Disability Score (RMDS) (152) was 14. The score can range between 0-24 (20, 25), while the Oswestry Disability Index (ODI) (191) mean score was 43 (21, 22). The ODI score ranges between 0-100. The mean pain intensity score from the three studies was 5.8, with the possible ranges of pain intensity being between 0-10 (22, 25, 190). For all measures, the highest score identifies the greatest disability and pain.

The mean EQ-5D-3L (87) score ranged from 0.26-0.49 (21, 22, 25). Generally, the possible ranges for the EQ-5D-3L are between 0 and 1, where high scores mean better health status. A further generic health status measure, the Short Form 6D (192), was also used in conjunction with EQ-5D in one study (22). One study looked at costs from the patient and healthcare provider perspectives (21), while the remaining studies were conducted from the societal perspective (20, 22, 25, 26). The length of follow-up was between 12 and 24 months.

The PMS in the included studies consisted of combinations of cognitive behavioural therapy, physical therapy and workplace interventions. Regarding the comparators, two studies compared PMS with usual care (20, 26), two with surgery (21, 22) and one with physical treatment and graded activity (a treatment that includes behavioural and cognitive methods to improve activity endurance) (two comparators) (25). The outcomes were return to work (20, 26), quality adjusted life years (QALYs) using EQ-5D-3L (21, 22, 25) and disability using RMDQ (25) and ODI (21, 22).

4.3.2 Methodological design

All of the economic evaluations were conducted alongside RCTs. The risk of bias assessment of the included studies is described in Table 4-2. Two of the five studies were considered to have low risk of bias (20, 25). The major strengths in all of the included studies were that the methods of randomisation and allocation were clear. Moreover, intention-to-treat analysis was considered in the statistical analysis for missing data. Finally, the timing of the outcome assessment was similar in the intervention and comparator groups.

Table 4-2 Risk of bias assessment according to the Cochrane Back Review Group (CBRG)

Risk of bias item	Skouen 2002 (26)	Rivero-Arias 2005 (21)	Smeet 2009 (25)	Lambeek 2010 (20)	Johnsen 2014 (22)
Was the method of randomisation adequate?	Low	Low	Low	Low	Low
Was the treatment allocation concealed?	Low	Unclear risk	Low	Low	low
Was the patient blinded to the intervention?	Not possible				
Was the care provider blinded to the intervention?					
Was the outcome assessor blinded to the intervention?					
Was the dropout rate described and acceptable?	Low	High	Low	Low	Low
Did the analysis include intention-to-treat analysis?	Low	Low	Low	Low	Low
Are the study reports free of suggestion of selective outcome reporting?	Unclear risk	Unclear risk	Unclear risk	High	Unclear risk
Were the groups similar at baseline?	Unclear risk	Low	Low	Low	High
Were co-interventions avoided?	Unclear risk	High	High	Unclear risk	Unclear risk
Was the compliance acceptable in all groups?	Unclear risk	High	High	High	Unclear risk
Was the timing of outcome assessment similar in two groups?	Low	Low	Low	Low	Low
Summary risk of bias	HIGH	HIGH	LOW	LOW	HIGH
Unclear = item not reported clearly. The study will be considered to have a low risk of bias if 6 or more items are satisfied, otherwise it will be considered to have a high risk of bias.					

Studies with high risk of bias had limitations (21, 22, 26). Two studies reported that the intervention group received extra visits to physiotherapists and other healthcare professionals compared with the standard care arm (21, 25). Hence, the intervention group might have had better outcomes, compared with standard care, because of these additional visits. One of the important aspects in assessing the quality of RCTs is the sample size and statistical power (193). Four out of five studies were sufficiently powered to detect a difference in functional disability using the ODI (21, 22), RMDS (25) or return to work (20).

Although all included studies incorporated RCTs, randomisation by itself does not ensure that the baseline characteristics of the study participants in the comparator groups are similar (193). Knowing this information is essential to demonstrate that the participant response to treatment is directly attributed to the intervention effect and not to other patient-related factors. Adjusting effect size for baseline characteristics should be performed using statistical methods, generally regression. In our review, only one study (25) performed regression to adjust effect size for baseline characteristics. Furthermore, two studies clearly reported that there was a significant difference between the study participants at baseline, which they did not then go on to adjust (22, 26).

The quality of reporting economic evaluations in terms of costs and outcomes is reported in Table 4-3, while the details of sensitivity analysis and the results are summarised in Table 4-4

Table 4-3 Assessment of economic evaluations based on CHEERS criteria (inputs to economic evaluation: costs and outcomes)

Study ID	Currency/year	Direct cost	Indirect costs	Time horizon	Health outcome	Valuation of preference outcomes
Skouen 2002 (26)	Norwegian Krone, price of clinic in 1996, no inflation	Top down approach	Yes	26 months	Return to work	NA (utilities were not collected)
Rivero-Arias 2005 (21)	2002-2003 GBP inflated to base year (2005)	Yes, unit cost from the lead investigating centre plus 15% overhead rate	Yes. costing total hours worked by each patient	24 months	Return to paid employment, total hours worked, utility using EQ5D	Social tariff from representative sample of UK population
Smeet 2009 (25)	2003 Euros	Yes	Yes, using human capital approach	12 months	Disability using RMDQ utility using EQ5D	AUC, population and techniques were not described
Lambeek 2010 (20)	Index year 2007 (Euro converted to GBP)	Yes	Yes, using human capital approach	12 months	Return to work utilities using EQ5D	Dutch tariff however no description of population or methods used
Johnsen 2014 (22)	Norwegian Krone with 2006 as a base year. Costs were adjusted for inflation into 2012 prices and converted to Euros using the rate 1 €=6.7 Kr2006	Top-down approach	Yes, using human capital approach	24 months	Utilities using EQ5D and SF-6D	QALY was estimated as AUC using trapezoidal method. Population and techniques were not addressed.

AUC = area under the curve, CE = cost effectiveness, CB = cost benefit, CU = cost utility, QALY = quality adjusted life years, EQ5D = EuroQol 5 dimensions, SF-6D = Short Form 6 dimension, GBP = British pound, NA= not applicable.

Table 4-4 Economic evaluation based on CHEERS criteria (statistical analysis and results)

Study ID	Statistical analysis of cost data	Statistical analysis for missing data	Incremental economic analysis reported	Sensitivity analysis	Difference in outcome	Difference in costs	Difference in outcome and costs
Skouen 2002 (26) Norway	Not reported, only mean difference in outcome evaluated by ANOVA. RR and 95% CI for the effect of intervention versus comparator on outcome.	Not reported	For men only, using light MDT, productivity gain = NoK 7858100 - cost, the net productivity gain = 240900	Not performed	Yes	Not reported	No
Rivero-Arias (21) 2005 UK	Arithmetic mean for cost and outcomes because skewness was modest, parametric tests were used.	Intention to treat and multiple imputation (variance correction)	Bootstrapping (1000 replications)	Yes	No	Yes	Yes
Smeet 2009(25) Netherland	Bootstrapping (1000 replications) student t test for change in outcomes, linear regression to adjust for baseline differences	Intention to treat analysis, missing data were replaced by mean score of cost and utility	Bootstrapping (1000 replications)	Yes	No	No	No
Lambeek (20) 2010 Netherlands	Not reported	Intention to treat analysis, multiple imputation	Bootstrapping (5000 replications)	Yes	Yes	Yes	Yes
Johnsen 2014 (22) Norway	Student t test for cost and utilities	Intention to treat analysis, multiple imputation	Bootstrapping (10,000 replications)	Yes	Yes	Yes	Yes
ANOVA = analysis of variance, RR = relative risk, CI = confidence interval, MDT = multidisciplinary treatment, NoK = Norwegian Krone							

4.3.3 Design and description of pain management services

The studies were delivered in a secondary care setting only (21, 22, 26), primary care only (25), or a combined setting (20). All the studies clearly described the service in terms of treatment modalities and the staff involved in delivering these services. However, in some studies the duration of treatment varied between people within the study (20, 22). In another study, the intensity of treatment in terms of the total hours provided was not consistent between people (21). Study participants were generally working-age adults; two studies focused on employees with CLBP(20, 26) and no studies included people above 65 years old..

The service description in the included studies is summarised in Table 4-5.

Table 4-5 Service description in the included studies

Study ID	Staff delivering the intervention	Intervention description	Number of hours/day and duration	Notes
Skouen 2002 (26) Norway	PT Nurse Psychologist (if necessary)	Light intervention: Assessment, a lecture, three individual sessions and individually-based graded exercise.	Assessment (1-2 hours) Lecture (1 hour) Total for individual sessions (45 minutes)	Some people were offered visits to an external PT, local National Health Insurance and workplace visits.
		Extensive intervention: Educational sessions, exercises and (occasional) workplace intervention	6 hours, five days a week for four weeks.	
Rivero-Arias 2005 (21) United Kingdom	PT and clinical psychologist	Education Exercises and hydrotherapy	5 days a week for three weeks The total hours were 60-110 (75 hr on average)	One of the centres did not have a psychologist or hydrotherapy sessions.
Smeet 2009 (25) Netherlands	PT Clinical psychologist or social worker	Physiotherapy Graded activity with problem-solving training	Physiotherapy: 105 min three times a week for 10 weeks Graded activity: 19 sessions starting from 3rd week.	
Lambeek 2010 (20) Netherlands	Occupational therapy physician PT, OT and medical specialist	Workplace intervention Graded activity	Graded activity (26 sessions) for three months or until RTW	Coordinated
Johnsen 2014 (22) Norway	PT Specialist in physical medicine	Lectures and individual discussions Daily workout	60 hours over 3-5 weeks	Nurse, psychologist or social worker as needed
PT= Physiotherapy, OT= Occupational therapy				

4.3.4 The comparator

Two studies, which were conducted in the Netherlands and Norway, compared PMS with “standard care” (20, 26). In Lambeek et al., standard care consisted of family physician visits, in addition to occupational therapist consultations, provided in a primary care setting (20). In Skouen et al., standard care consisted of examination in the spine outpatient clinic by a physician, followed by referral back to the GP (26).

Two studies compared the effect of PMS with surgery (21, 22). The surgical procedures were total disc replacement (22) and spinal stabilisation (21). As surgical options are usually reserved for more severe cases, the patient populations in these studies are likely to be different from those where GP management is offered as standard care (25, 26, 190). The mean utility scores assessed using EQ-5D at baseline were 0.26 and 0.49 in a study assessing surgery (22) and non surgical treatments (25) as comparators, respectively. Similarly, the pain intensity score was 6.9 in the study assessing surgery (22), while in the study assessing SC, the score was 5.7 (20).

4.3.5 Healthcare resource use and cost

In this review, all of the studies included direct medical and indirect costs. Four studies included direct non-medical costs, such as complementary and alternative therapists, travel expenses and over-the-counter medicines (20-22, 25). Four studies took the societal perspective (20, 22, 25, 26) and one study took the healthcare provider perspective (21). Although the last study stated that they conducted their evaluation from a healthcare provider perspective, indirect costs were calculated. Although

Skouen et al. stated that their study took a societal perspective (26), direct non-medical costs were not collected.

There are two methods of assessing the service costs, the top-down and the bottom-up (micro-costing) approaches (63). The top-down approach divides the total budget of a health intervention by the total number of people to give an "average" estimate of cost per patient, whereas the bottom-up approach uses patient-level resource use data to generate costs. The latter is the preferred method in economic evaluations to account for variations in costs between study participants (63). In this review, three studies used the top-down approach (22, 25, 26), while two studies used the bottom-up method (20, 21). The method of collecting costs was implied, rather than clearly stated, in three studies (21, 25, 26). Only two studies clearly reported all resource use and their unit costs, which included direct medical, direct non-medical and indirect costs (20, 25). In the other two studies, some unit costs were missing (21, 22) and Skouen et al. did not report unit costs (26).

In this review, two studies used postal questionnaires to collect resource use data from people (20, 21), which might be subject to recall bias, especially if the recall period is more than three months (194). In Lambeek et al., the recall period was three months (20) while, in Rivero-Arias et al., the recall period was six months and one year (21). The other two studies used costing diaries to collect resource use data (22, 25). Costing diaries aim to collect data prospectively, which reduces the risk of recall bias. In order to minimise the risk of incompletion, regular telephone reminders are recommended but neither of the studies using diaries provided reminders (22, 25).

Productivity loss due to illness can be accounted for by absenteeism, the inability to attend work, and presenteeism, the reduced functionality in terms of quality and quantity while working (67, 68). Productivity loss can be measured either objectively, by using health insurance registries, or subjectively, using self-report by the employee (67). These methods have some limitations; objective measures might be inaccurate for assessing presenteeism, as they only record employee attendance, with no emphasis on productivity levels in terms of quality.

In this review, all of the studies assessed the effect of PMS on productivity loss. Absenteeism was the only work outcome evaluated. Among the included studies, four studies clearly reported their methods of collecting productivity loss outcomes (20, 21, 25, 26). Two studies used "monthly" self-reported methods, such as calendars (20) and diaries (25). In another study (21), the employment status was self-reported over a relatively long period of six months and one year. Zhang et al. stated that, although the appropriate recall period is still inconclusive, three months' recall for absenteeism and one week for presenteeism is recommended (67).

The long recall period and insufficient information about the measurement method might lead to an inaccurate estimate of productivity loss in this study (21). An objective measure was used in one study (26), which utilised the national health insurance registry to assess sickness absence. Johnsen et al. (22) did not report the method of data collection.

In order to value productivity loss among employees, the “human capital approach” and the “friction cost method” can be used (67). The definition and limitations of each method are described in the literature review (Section 2.5).

Four studies used the human capital approach to value productivity loss (20, 22, 25, 26). None of the included studies assesses the productivity loss using both methods in order to determine levels of variation of costs derived from the two approaches.

4.3.6 Statistical analysis

The statistical analysis of patient-level cost data needs to be adjusted from standard approaches as cost data is generally “positively skewed”, because a small number of people usually require more healthcare resources (63, 182). Non-parametric tests rely on medians and distributional shape and the transformation often used for this type of data distribution might provide misleading estimates, as these tests cannot produce “arithmetic means”. Non-parametric bootstrapping with replacement is the preferred method to analyse cost data because it compares arithmetic means while avoiding distributional assumptions. Standard parametric tests can be used to analyse cost data only if the sample size is large, where skewness will not affect the validity of the analysis. Barber et al. reported that, for sample sizes larger than 150 participants (195), the t-test is usually robust and valid, as parametric assumptions will generally hold. In this review, two studies used non-parametric bootstrapping to test the difference in cost (20, 25), whereas two studies with larger sample sizes, 349 (21) and 173 (22), used parametric t-tests for cost analysis. Skouen et al. did not analyse differences in costs (26).

Discounting is a calculation used to estimate the value of outcomes and cost in the future (63). This concept is important in economic evaluation because present outcomes and costs are considered more valuable than those in the future. Therefore, future costs need to be discounted in interventions that last for more than one year. In this review, three studies had interventions that continued for two years (21, 22, 26), two of which reported the discount rate according to the country specific rates (21, 26).

4.3.7 Dealing with uncertainty

The incremental cost effectiveness ratio (ICER) is the main summary measure of an economic evaluation and is calculated by dividing the difference in cost by the difference in effect (outcome) between two interventions (63).

In addition, sensitivity analysis is needed to test the validity of the results by changing the value of certain parameters used in the base case analysis (63, 182). The base case analysis is the first step of an economic evaluation in which outcome and cost data generated from the study is used to estimate the cost effectiveness of the intervention. In one-way sensitivity analysis, one parameter is changed at a time to test the results, whereas multiple-way analysis changes multiple parameters at the same time. Although one-way sensitivity analysis is easy and understandable, it can underestimate total uncertainty in the ICERs (196).

Probabilistic sensitivity analysis (PSA) assumes that the values of certain variables have a probability distribution. Probabilistic incremental economic analysis is usually carried out using bootstrapping to generate credibility intervals that provide a quantitative measure of uncertainty around ICER point estimates. For the graphical

representation of ICERs, cost effectiveness planes are used to present the distribution of bootstrapped ICERs (63). Another common graphical presentation used in economic evaluation is the cost effectiveness acceptability curve (CEAC) (63). The CEAC is a technique for representing information on uncertainty in cost-effectiveness. A CEAC demonstrates the probability that an intervention is cost-effective compared with the substitute, given the observed data, for a range of maximum monetary thresholds that policy makers are willing to pay for a specific unit change in effect (197). In this review, four studies generated ICERs using bootstrapping (20-22, 25) and three of them presented ICERs on cost effectiveness planes (20, 22, 25). CEACs were used in these studies to present the probability of cost effectiveness (20-22, 25). These studies all carried out further one-way sensitivity analysis.

4.3.8 Cost-effectiveness of PMS

The ICERs generated by the studies are summarised in Table **4-6** . Only one study concluded definitively that PMS dominates usual care (20). Skouen et al. concluded that multidisciplinary services are cost-effective in men only (26). However, this conclusion needs to be interpreted with caution given that top-down costs were used and there was no sensitivity or statistical analyses. Two studies reported that PMS are cheaper and less effective than surgery (21, 22). Therefore, a trade-off between cost and effect needs to be considered. Smeet et al. compared PMS with active physical treatment (APT) and graded activity plus problem solving (GAP) (25). In this study, the PMS was dominated when compared with GAP, while it was cheaper and less effective when compared with APT.

Table 4-6 Summary of incremental cost effectiveness analysis results

Study ID	Intervention/Comparator	Outcome measure	Cost difference	Outcome difference	ICER	Notes
Skouen 2002 (26) Norway	Multidisciplinary treatment vs usual care	Return to work	Not reported	Net productivity gain NoK 7858100 (USD 924500)	For men only using multidisciplinary treatment: Net productivity gain = NoK 7240900(USD 852000)	
Rivero-Arias 2005 (21) UK	Intensive rehabilitation vs surgical stabilisation	QALY	- £3304	- 0.068	48588 £ per QALY	Cost effectiveness threshold 20,000-30,000£ per QALY
Smeet 2009 (25) Netherland	Combined treatment vs active physical treatment	RMDS	- €456	- 1.23	371 € per one point reduction in RMDS	
		QALY		0.014	35060 € per QALY	
	Combined treatment vs graded activity plus problem solving	RMDS	€4765	- 1.27	-3759 € per one point reduction in RMDS (dominated)	
		QALY		- 0.045	-108857 € per QALY (dominated)	
Lambeek 2010 (20) Netherlands	Integrated care vs usual care	Return to work (days)	£217 (direct cost)	- 68	-3* £ per one day earlier return to work	
		QALY	- £5310 (total cost)	0.09	-6100* £ per QALY (dominant)	
Johnsen 2014 (22) Norway	Multidisciplinary rehabilitation vs total disc replacement	QALY using EQ-5D	- €13506	- 0.34	39748* € per QALY	Cost effectiveness threshold €74,600 per QALY
		QALY using SF-6D		0.11	128328 € per QALY	
*Cost effective, NoK = Norwegian Krone, QALY = quality adjusted life years, USD = United States Dollar						

4.3.9 Economic evaluation using decision analysis models

In this systematic review, one of the aims was to identify decision analysis models in order to inform the economic model to be developed to examine the cost-effectiveness of the Nottingham PMS. The key elements in the economic model structure, including health states, transition probabilities, effectiveness parameters, healthcare resources and costs, were needed to inform the economic model in Chapter 5. However, no decision analysis models were identified in this review. Decision analysis has some advantages over economic evaluation alongside RCTs. Firstly, the lifetime cost effectiveness of the intervention can be assessed and, secondly, in the absence of a completed comparative study at the time of decision making, it can provide the decision maker with an indication of probability of cost-effectiveness in a timely manner (198). In addition, this method allows for a comparison of all available treatment options. Finally, a decision analysis model can incorporate the best available evidence from the meta analyses and RCTs to provide the most valid estimates of the model inputs.

From this review, the studies' follow up periods were short (2 years), which is not sufficient to assess the differences in clinical and economic outcomes. In addition, studies assessing PMS compared with SC in the UK were lacking. The results of the long-term cost effectiveness of the PMS from the UK NHS perspective is fully described in Chapter 5.

4.4 Discussion

To our knowledge, this is the first systematic review that summarises the current evidence regarding the cost-effectiveness of PMS in CLBP.

This systematic review showed that these services might be cost-effective. However, conclusive statements about cost effectiveness cannot be made for a number of reasons. Firstly, the complex nature of these interventions, in terms of number and diversity of healthcare professionals working in an integrated approach, leads to the multidimensionality of the achieved outcomes, which leads to difficulty in assessing the cost effectiveness of these interventions.

Secondly, the comparators among the included studies varied considerably, which leads to difficulty in drawing useful conclusions. In addition, the studies included in the review were conducted in both primary and secondary care settings, which might suggest that the characteristics of people in each setting are different and, thus, the response to the PMS would also be different.

Thirdly, the restriction in inclusion criteria in some studies was limited to working adults, which might limit the generalisability of these services to the general population, which include homeworkers, the unemployed and older adults. A trade off between increasing the generalisibility of studies while limiting the heterogenity by focusing on a specific subset of people with CLBP need to be considered. This can be achieved by using pragamtic RCTs.

Given that this was the first systematic assessment of the cost effectiveness of PMS for people with CLBP, we did not restrict the study participants' inclusion criteria in order to have a better insight about the effectiveness of these services in the general population. These challenges are augmented by the heterogeneity of back pain, which is as a result of its complex underlying aetiology and clinical course (128) and psychosocial factors that might influence the progression of the condition.

In this review, three studies out of the five have a high risk of bias, which is caused by limitations in the methodological design of the RCTs. This finding is consistent with a Cochrane review published by Kamper et al. (15). This systematic review of the effectiveness of PMS in CLBP included 41 studies, of which 28 studies were considered to have a high risk of bias. Generally, most systematic reviews assessing back pain interventions report that the majority of the eligible RCTs have methodological limitations that lead to a high risk of bias and, subsequently, the conclusions are often not underpinned by robust evidence (199).

In this review, all the economic studies were conducted alongside RCTs and the follow-up period ranged from one to two years. Although this length of follow-up gives some idea of the "downstream medical cost" associated with long-term treatment, ideally longer follow-up (lifetime horizon) is needed. According to the MRC recommendations for complex intervention evaluations (200), a lifetime horizon is needed to demonstrate the sustainability of short term changes in outcomes.

Several shortcomings were found in estimating the cost of the PMS. Using a top-down approach gives the average cost per patient; however, the method is not useful in

estimating the cost of people who consume healthcare resources more or less than average patients do, such as people with mild or severe conditions, and, therefore, underestimates the cost of the intervention. Unit costs were either poorly reported or not reported at all.

Apart from methodological limitations in the economic evaluation study design, several problems are generally encountered when conducting systematic reviews of complex interventions. Guise et al. reported that terminology is one such barrier (201). Service terminology is highly variable across different settings, countries and clinical contexts and this factor might increase the difficulty in searching and identifying relevant publications.

Researchers who are interested in conducting systematic reviews in complex interventions need to select between an inclusive search that gathers a wide range of heterogeneous studies to inform the literature about factors that influence this heterogeneity and, thus, address these limitations for future research, or use strict search criteria that define the intervention clearly, which can result in a robust conclusion. However, conducting such a review might be difficult as researchers might struggle with terminology. In addition, narrowing the research might result in a small number of studies, given that the type and intensity of treatments provided within PMS are highly variable. The chance of finding studies that have an identical service, in terms of staff, disciplines involved, duration and intensity, is unlikely.

In this systematic review, a broad search criterion was chosen to conduct the systematic review because the main objective was to investigate the cost effectiveness

of the PMS regardless of the type or the intensity of the treatments provided. Although it is logical to compare interventions that have the same components to assess cost effectiveness, it is rare to find studies comparing a matching intervention.

Given these challenges, inconclusive results about the cost effectiveness of these services arise from the variability and heterogeneity of the services and the condition respectively, which makes comparison between studies difficult. The other issue is the poor quality of RCTs, which are the source of "effectiveness data" in economic evaluation, leading to weak cost effectiveness results. Finally, the limitations in estimating the cost of services and the short follow-up period affect the results of the economic evaluations.

The type of services described in this review are not comparable with the PMS provided in Nottingham. Services in the included studies were standardised in terms of the type of treatment modalitites given and the number and intensity of sessions, whereas PMS in our setting is individualised and tailored based on the patients' needs and their previously given treatments.

Economic evaluations discussed in this chapter were alongside RCTs with a short follow-up period, which is insufficient to assess the long term benefit of the service. Decision analysis models, which usually have lifetime cost effectiveness data, were lacking. In addition, a study assessing this PMS compared with SC in the UK was missing.

4.5 Conclusion

PMS might be cost effective in the management of CLBP. However, this systematic review highlights the discrepancies in the evidence supporting PMS for people with CLBP due to the variability of the interventions, comparators and outcomes. Therefore, better studies are needed, as decisions should not be made based on these studies.Research directions should focus on optimising the methods of assessing healthcare resource use and cost in order to improve the analysis in the future. In addition, there is a need to study the long terms benefits of these services by conducting pragmatic RCTs combined with model-based economic evaluations.

Chapter 5

Constructing a Markov Model to Evaluate the Cost Effectiveness of a Pain Management Service Compared with Standard Care for Adults with Chronic Low Back Pain

5.1 Introduction

Evaluating the cost effectiveness of the PMS is important in deciding whether this type of service should be funded by the National Health Service (NHS) or should be decommissioned before being more widely implemented. The paucity of evidence regarding the cost effectiveness of these services (Chapter 4) prevents decision makers responsible for resource allocation from approving the most efficient management strategy for people with CLBP. As these services are resource intensive, one consideration is that they might have additional costs for the NHS. However, better clinical outcomes might improve pain intensity and quality of life, which might have an impact on healthcare resource use.

In this chapter a decision model is developed, informed by the published literature, expert opinion and the service evaluation study, described in Chapter 3. To our knowledge, no previous decision analysis models have been published that are used to evaluate the cost effectiveness of PMS in CLBP.

The aim of this study is to evaluate the cost effectiveness of a PMS, compared with SC, for CLBP in adults, from the perspective of NHS England, using a decision analysis approach.

5.2 Objectives

The objectives of this study are to:

1. Build a decision analysis model to compare a pain management service with standard care.

2. Identify, quantify and analyse the incremental cost and benefits of a pain management service compared with standard care.

3. Quantify the uncertainty around the incremental costs and benefits of a pain management service compared with standard care.

5.3 Methods

5.3.1 Intervention and Comparator

To construct the treatment pathways for an economic model, it is essential to describe SC and the PMS. This includes a description of the patient's point of entry to the intervention or comparator, the key components of the intervention and the comparator, namely the index consultations and follow-up, commonly used referral options from and to the PMS, the use of clinical assessment, triage and clinical management of patients. Descriptions of typical treatment pathways were obtained from GPs who worked in collaboration with the PMS. The aim of these of interviews was to describe the treatment pathways in standard care and PMS, standard care being the type of treatment provided before establishing the PMS. An interview guide contained several questions regarding the types of treatment provided, the duration, the referral criteria to secondary care and to the PMS. Three GPs were interviewed. The first interview was with Dr. Kelvin Lim (Clinical Lead of the Primary Integrated Community Services in Nottingham and GP at Church Street Medical Centre, Eastwood, Nottingham) and Dr. Kerri Sallis (GP at Balderton Primary Care Centre, Newark, Nottingham). The second interview was with Dr. Nicole Atkinson (GP at Church Street Medical Centre, Eastwood, Nottingham).

5.3.2 Pain Management Service Pathway

People with CLBP are managed by their general practitioner (GP). The GP recommends maintaining as much physical activity as possible, back exercises and analgaesics and monitors the patient. People who have “red flag” signs, such as cancer, are referred directly to secondary care. People reporting “yellow flag” signs, such as inability to work or severe disabling pain, and who do not improve after approximately three months’ treatment are referred to the PMS.

People have a single consultation with one of the members of the PMS team (including a pain consultant or an advanced physiotherapist) (33). After initial assessment, a treatment plan is tailored based on the patient’s needs. The PMS member either discharges the patient with modifications to the analgaesic regimen and the GP follows up with the patient, or refers the patient for magnetic resonance imaging (MRI) or facet joint injections. Otherwise people might require referral to a community-based physiotherapist, an occupational therapist or an acupuncturist. Then, people are discharged from the PMS after having this single consultation.

After completing the treatment plan designed by members of the PMS team, the people continue their follow-up with their GPs. If a patient’s clinical condition remains unchanged or worsened, the GP can refer the patient back to the PMS to revise the treatment plan. The pathway is illustrated in Figure 5-1.

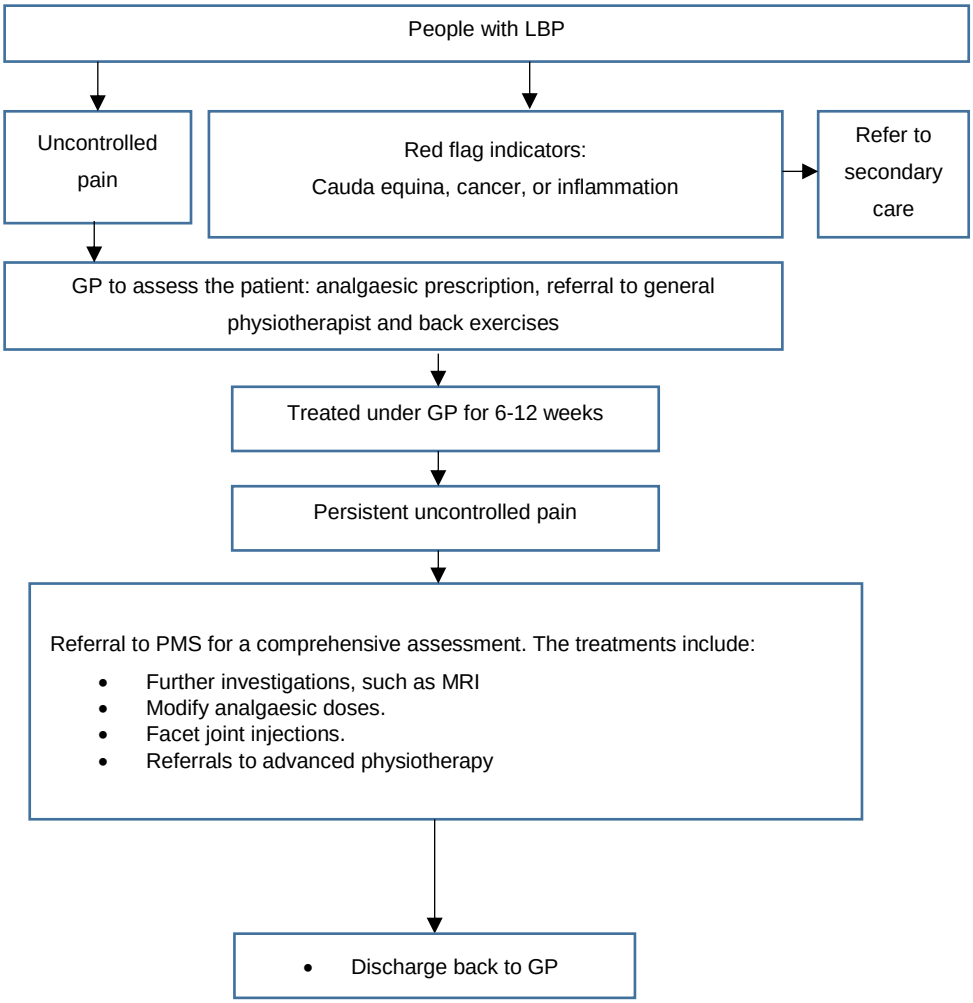


Figure 5-1 PMS pathway

5.3.3 Standard care pathway

Prior to development of the PMS, SC involved GP treatments, which includes back exercises, pharmacological treatment and referral to physiotherapy. If the GP is not entirely confident about the management and/or the patient is reporting severe, disabling pain, the GP refers the patient to secondary care. The main specialties for CLBP are spinal surgery or neurosurgery. If the patient is not a candidate for surgery, they are discharged from secondary care and referred back to their GP. The standard care pathway is illustrated in Figure 5-2.

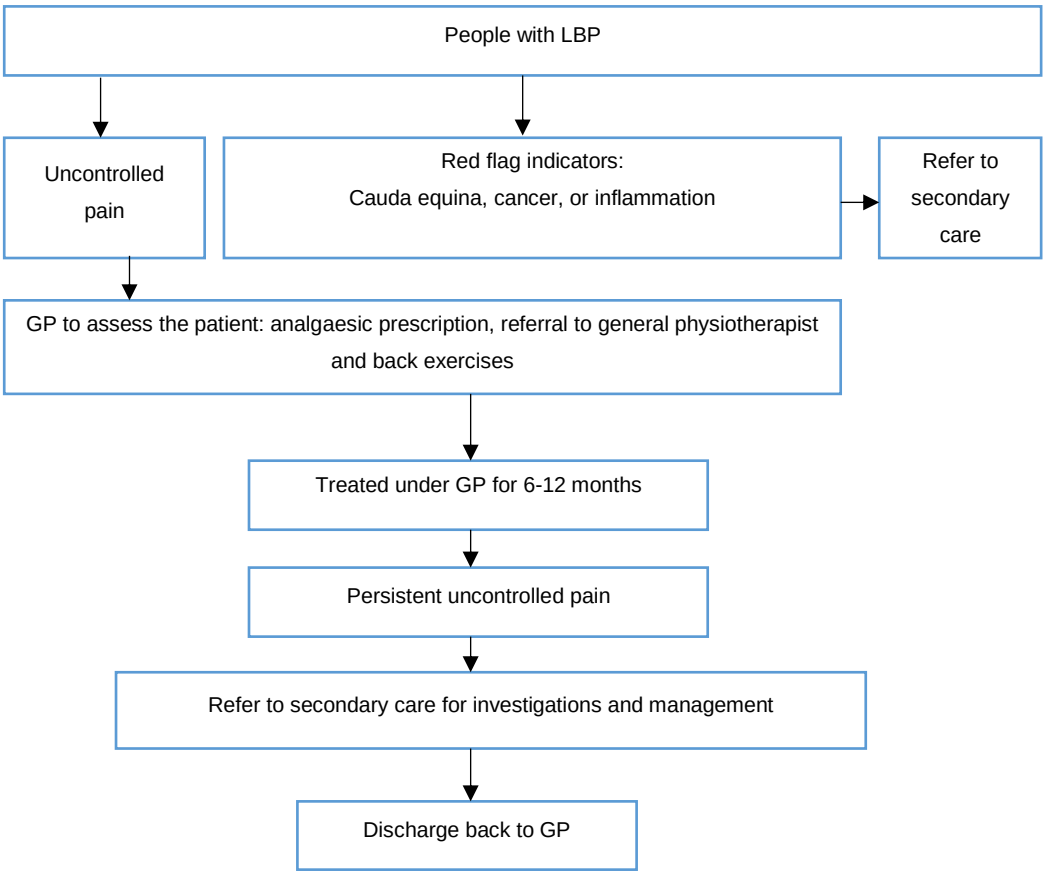


Figure 5-2 SC pathway

5.3.4 Study population

The cohort study in Chapter 3, which described the PMS in Nottingham, was used to define patient characteristics at baseline. The total number of people was 32. The mean age was 58.8 (range 32 to 87) years with equal distribution of both genders. The study characteristics of our cohort are similar to previously published studies assessing several interventions for people with back pain (202, 203). People in the economic model were assumed to present with the same distribution of pain intensity as this cohort. The initial pain intensity distribution is summarised inTable 5-1.

Table 5-1 Initial distribution for people with CLBP

Pain levels	**n (total n=32)**	**Probability**
Mild	7	0.21
Moderate	24	0.65
Severe	4	0.12

5.3.5 Structure of the Economic Model

The purpose of the model is to identify and quantify the incremental cost and benefits of the PMS compared with standard care for adults with CLBP. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria were followed to design and report the economic model (189).

A Markov model can be used to simulate the natural progression of chronic conditions (204-206). However, one of the key limitations of Markov models is the memoryless aspect of the health states, which means that the transition probabilities of the cohort rely upon the present health state and not on the preceding one (204-206). These

limitations can be conquered by changing the transition probabilities according to the time the cohort spends in the model (206, 207).

Other types of decision analysis models that can be used are decision trees and discrete event simulation (DES). Decision trees are the simplest type of economic models (207, 208). However, they become complex to use in chronic conditions because they necessitate that all the events that repetitively happen during the course of the disease are incorporated in the tree. Therefore, the tree requires many branches, which will lead to complexity in analysis (207-210). DES can be used when people are competing for the same constrained resources or interact with each other. A DES model can also be used when patients' characteristics affect the possibility and timing of a subsequent event. One of the shortcomings of this model is the requirement for data (207). Hence, for this economic evaluation, a Markov model was considered the most suitable modelling approach to simulate the clinical course of CLBP.

To construct a Markov model, health states, cycle length, transition probabilities and a time horizon need to be defined and specified. In addition, utility scores and costs must be assigned to each health state.In this model, health states are defined based on levels of pain intensity, as this directs treatment choices in CLBP more than any other health status measure, and can be linked directly to health status (utility) and costs. Ability of interventions to move people from higher to lower levels of pain intensity are accepted measures of effectiveness in people with CLBP. The specific measure used to define the level of pain intensity was the Brief Pain Inventory (BPI) pain intensity score (95). This measure was selected because of its tested validity and

responsiveness to changes in CLBP (211-214). The BPI assesses pain intensity using an 11-point linear scale, which covers four pain domains: “worst pain”, “least pain”, “average pain” and “pain right now”. The pain intensity is calculated as the mean score of these four domains. Having an mean score of these individual domains of pain increases the accuracy of the overall measurement of pain, unlike the numerical rating scale (NRS) and the visual analogue scale (VAS), which measure pain using a single question and, therefore, do not represent the nature of pain experience or improvement due to symptom fluctuations (215).

Figure 5-3 shows a schematic representation of the patient pathway. The model structure is built as a standard decision tree followed by a Markov model, using TreeAge (TreeAge Software Inc, One Bank Street, Williamstown, MA, 01267, USA) (216). The decision tree represents two treatment options, the pain management service and the standard care. The model consists of three health states, mild or no pain, moderate pain and severe pain. Pain intensity scores between 0-4 were defined as mild pain, 5-6 as moderate pain, and 7-10 as severe pain (217). An additional, absorbing health state represents ‘death from all causes’, which the cohort can enter from all health states at any time.

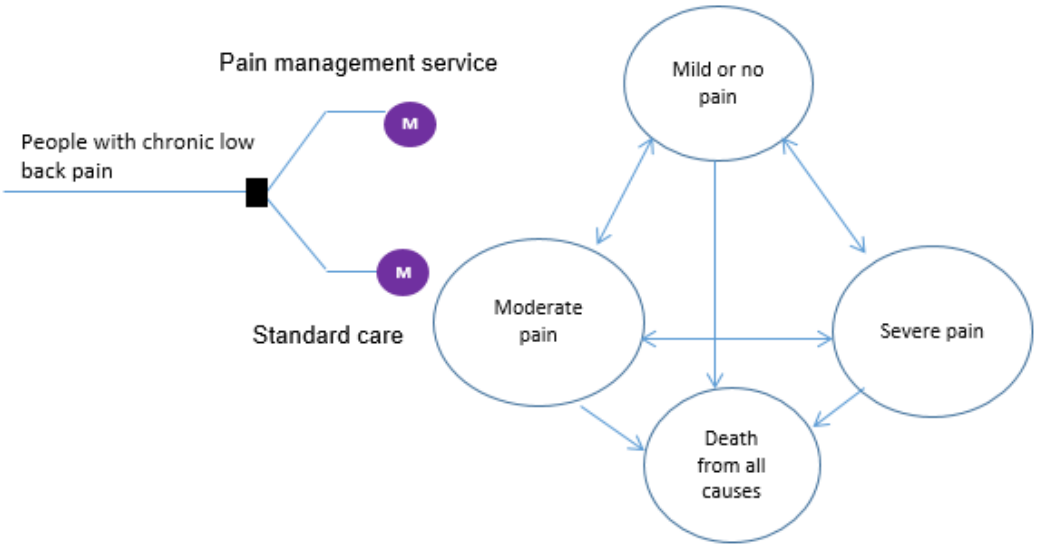


Figure 5-3 Decision analysis model for PMS economic evaluation

Evidence from the literature has shown that disabling CLBP can lead to an increased risk of mortality in older adults (age >75 years), when compared with the general population (218, 219). Moreover, another study showed that CLBP increased the risk of suicide (220). Therefore, we assume that people with severe CLBP are at an increased risk of death compared with people with less severe pain and this has been incorporated into the model. The details of severe pain-related increased risk of mortaility are discussed later in section 5.3.6.3.

The arrows on the Markov diagram indicate the transitions that people can make in the model. The transition probabilities governing the direction between health states in the model are explained later, in section 5.3.6.1. The structural assumption in this model is that, within one cycle (three months), the patient can remain in the same state, move to a lower or a higher pain intensity state, or die.

The cycle length and time horizon usually depend on the nature of the condition and the intervention, respectively. The model uses a three-month cycle length, which has been generally considered the most commonly used cycle length to reflect the disease course in CLBP. This cycle length has been used in published decision analysis models for CLBP (125, 221, 222). A lifetime horizon (up to 100 years of age) and the 3.5% discount rate for costs and outcomes recommended by the UK Treasury were used (223).

5.3.6 Data Sources for Model Inputs

Searches were performed to find the best available evidence in the literature to design and populate the model (transition probabilities, utilities, healthcare resource use and unit costs).

Two types of literature search were performed. A systematic review of the cost effectiveness of PMS was conducted (Chapter 4). The aim of this review was to find trial and model-based economic evaluations. However, only five economic evaluations alongside RCTs were found. From those five studies, one author was asked to provide patient-level data to derive transition probabilities and healthcare resource use data (20). However, the author did not agree to share his data. The four other authors were not approached as the comparator in their studies was different from the standard care arm in this economic evaluation (21, 22, 25, 26).

Therefore, a further literature review was carried out to find transition probabilities. A systematic review by Kamper et al., which aimed to assess the effectiveness of PMS in CLBP, was used as the first search step to identify relevant publications (15). In this

review, nine studies (n=433) compared PMS with standard care and reported pain intensity as an outcome. Among those studies which could be considered to be comparing an intervention and a standard care treatment option comparable to this study, Von Korff et al. (224) was considered the most favourable option, for several reasons. Firstly, it was the largest study in terms of sample size (n=240 patients). Secondly, although evidence suggests that the smaller studies tend to have a larger effect size compared with larger studies (225), Von Korff et al. had a conservative estimate of the effect size at three months (standardised mean difference (SMD)=0.2, 95%CI 0.46-0.05) compared with the overall effect size of the nine studies (SMD=0.55, 95%CI 0.83-0.28). In addition, the author agreed to provide us with patient-level data to derive transition probabilities.

Another search was performed to identify healthcare resource use and utilities. One of the challenges that was encountered when searching for relevant publications was the need to find the utility scores and health resource use stratified by pain intensity level. These data were needed in order to assign a cost and a utility score for each health state. Two large economic evaluations, alongside RCTs, fulfilled this criterion (202, 203, 226, 227). Although the STarT Back (203, 226) and IMPaCT Back studies (202, 227) were similar to each other in terms of intervention (stratified care), comparator (best practice), eligibility criteria and outcome measures, the IMPaCT Back study (202, 227) was chosen because the participants in the IMPaCT Back study were slightly older (mean=53, SD=15) compared with the STarT Back study (mean=50, SD=15), respectively, reflecting more closely the start age of the theoretical model cohort.

Preferably, a model should be designed to describe all treatment pathways related to the decision problem. Good practice guidelines for decision analysis modelling state that unavailability of data should not be a reason for not conducting a decision analysis model (228, 229). Treatment pathways and healthcare resource use were based on the IMPaCT Back study findings (202). Although this study was conducted in the UK, variation in healthcare resource use across the country is common; therefore, expert opinion from our locality is needed to address the pattern of healthcare resource use in the study and to discuss the similarities and differences between the study and our setting. Expert opinion is a standard possible source of data and is frequently used to complement insufficient data in the published literature (228, 230).

A group of GPs working closely with the service were interviewed to discuss healthcare resource use for people with CLBP managed in the primary care setting. The details of those GP are discussed in section 5.3.1. Further information about the results from these interviews is discussed in the healthcare resource use section 5.3.6.4.

In conclusion, three studies were used to populate the economic model: the service evaluation study, which is fully described in Chapter 3; the study by Von Korff et al. for transition probabilities (224) and the IMPaCT Back study for healthcare resource use and utilities (202) adjusted for local variation by expert opinion. The details of the data used are described below.

5.3.6.1 Transition Probabilities

The transition probabilities for the PMS and standard care were derived from an RCT conducted by Von Korff et al. (224). This study aimed to evaluate an activating

intervention that involved psychological therapy and physical exercise; this intervention was compared with the usual care for CLBP. The details of the Von Korff study are summarised below.

The Von Korff study was conducted in the primary care setting. Adults aged 25-64 years who had suffered CLBP were eligible. The study excluded people being candidates for back surgery or already being treated by physiotherapists or psychologists.

In this study, there were some restrictive inclusion criteria that might affect the generalisability of the findings, such as excluding people over 65 years old. Excluding people who were candidates for surgery or were being treated by a psychologist is a major strength, because those groups of people have other underlying conditions or psychological illnesses that might influence the effect of the intervention. A similar exclusion criterion was also applied in our cohort; therefore, both cohorts seem to be comparable in terms of including people with CLBP with no other underlying causes or confounding factors.

The intervention consisted of four visits. The first was a psychologist's visit aimed at addressing the patient's fear about CLBP. The second and third visits were to the physical therapist and consisted of back assessment, outlining an exercise treatment plan and then reinforcing the action plan; these visits were 10 days apart. The last visit was to the psychologist again, to review progress. The total duration of this intervention was 35 days. Usual care involved the use of prescription and over the counter medications, infrequent visits to the GP and referral to physiotherapy. The

dissimilarity between the interventions by Von Korff et al. (224) and the PMS in Nottingham was that the treatment plan in Nottingham is tailored to patients' specific needs, whereas the service evaluated by Von Korff et al. (224) provided a pre-structured intervention. Nevertheless, the SC in both settings was comparable.

In the intervention group (n=110), the mean age was 49.7 (SD=9) years and 64.7 % were female. Participants reporting moderate and severe pain represented 23% and 44% of the whole sample. There was no statistical difference between the intervention and control groups in terms of baseline characteristics. The dataset provided by Von Korff et al. contains demographic data and pain intensity scores at baseline, 2, 6, 12 and 24 months for both the treatment and the control group. In this dataset, the worst pain, pain right now and average pain scores were reported. The average score of these three domains were calculated to generate one score representing the average pain intensity in the BPI (95). STATA 11.1 (158) was used to analyse the dataset and to find the transition probabilities for each pain level category. The mean pain intensity score at twelve months was used to derive the transition probabilities. This time point was selected to estimate the long term effectiveness of the PMS.

Table 5-2 represents the preliminary transition probabilities for twelve months for both study arms. In order to use this data in our decision model, transition probabilities were transformed to match our study cycle length. The next section describes how the data was transformed to three-month transition probabilities to be used in the economic evaluation.

Table 5-2 Transition probabilities and the number of people in each health state at twelve months

Health states	PMS			Standard care		
Pain intensity	Mild	Moderate	Severe	Mild	Moderate	Severe
Mild %,(n)	0.77 (10)	0.15 (2)	0.08 (1)	0.67 (6)	0.33 (3)	0 (0)
Moderate %,(n)	0.67 (16)	0.25 (6)	0.08 (2)	0.50 (11)	0.46 (10)	0.04 (1)
Severe %,(n)	0.33 (3)	0.33 (3)	0.33 (3)	0.23 (3)	0.23 (3)	0.54 (7)

As the study performed by Von Korff et al. did not collect three-month data to match this study's cycle length, multiplying the two-month transition probabilities, for example, by 1.5 will not yield the required probabilities. Instead, the standard way is to derive rates and, from that, the 3-month probabilities are calculated. The rate is derived from transition probabilities and then is converted into probabilities for the period of interest, i.e. three months, using the following equations (231):

$$P = 1 - e^{-(rt)}$$

$$r = -[\ln(1 - P)]/t$$

Where P=probability, r=rate, t=time

A half cycle correction, by assigning half the reward in each state, was applied to both cost and effectiveness in the first and final cycle. Giving a full reward at the start (i.e., transitions occur at cycle end) overestimates expected values; assigning no reward (i.e., transitions occur at cycle start) underestimates them.

The three-month transition probabilities for both arms are summarised in Table 5-3.

Table 5-3 Transition probabilities in each health state at three months

Health states	PMS			Standard care		
Pain intensity	Mild	Moderate	Severe	Mild	Moderate	Severe
Mild	0.95	0.04	0.01	0.90	0.10	0
Moderate	0.24	0.74	0.02	0.16	0.78	0.06
Severe	0.46	0.10	0.45	0.06	0.06	0.87

5.3.6.2 Using Life Tables to Estimate All-Cause Mortality

The data regarding age-adjusted all-cause mortality rates was obtained from the Office for National Statistics in the UK for the latest available years (2014-2016) (232). A combined mortality for men and women was used. This data was incorporated in the model and, in every four cycles, i.e. one year increase in age, the rate of death increased, based on the age of the patient. The full table is in Appendix I.

5.3.6.3 CLBP and Increased Risk of Mortality

A literature search was performed to identify back pain-related mortality. The key words in this search were back pain, death and mortality. Another search was performed to look at mortality related to chronic pain in general. Four studies were identified (218-220, 233). Three studies were specific to CLBP (218-220) and one for chronic pain (233).

Docking et al. investigated the effect of disabling CLBP on mortality in 1174 older adults (≥ 75 years) (218). Disabling pain was defined as pain that has interfered with daily tasks in the last month. The study showed that disabling CLBP is strongly associated with mortality in older adults (HR 1.4, 95%CI: 1.1-1.8) and this association

remained borderline significant after adjusting for potential confounders (HR 1.3, 95%CI: 0.99-1.7). Another study by Zhu et al. assessed the effect of CLBP on mortality in 1484 elderly Australian women (70 to 85 years of age) (219). The study found a significant association between CLBP and death and daily CLBP was associated with a greater overall mortality risk (HR = 2.03; 95%CI, 1.14-3.60).

Ilgen et al. investigated the effect of pain conditions on the risk of suicide in the US (220). The study included 4,863,086 patients, 22.8% of whom were diagnosed with CLBP. After adjusting for confounding variables, people with CLBP were found to have a higher risk of suicide compared with the general population (HR= 1.33 ;95% CI, 1.22-1.45). The last study by Torrance et al. aimed to investigate the association between chronic pain and 10-year mortality (233). The study included people with a wide range of pain conditions, with arthritis and CLBP representing 46.4% and 33.3% of the sample, respectively. The remainder of pain-related diagnoses included angina, cancer, other causes or unknown causes. The results showed that people reporting severe pain are less likely to survive than those reporting mild pain. After adjusting the confounder factors, the HR was 1.49 (99%CI: 1.21-1.84). However, this study is not specific for CLBP so, therefore, this figure should be extrapolated to CLBP with caution.

Based on these previous studies, Docking et al. (218) and Ilgen et al. (220) are the best available option to derive mortality related to back pain. The study by Docking et al. was conducted in the UK and, therefore, patients' characteristics might be similar to our cohort in terms of disease progression patterns. Ilgen et al. was the only study

investigating the risk of suicide among people with chronic pain. In addition, the sample size for CLBP (n=1111187) was larger compared with Torrance et al. (n=1377).

The evidence from Zhu et al. cannot be used as their study was conducted among elderly Australian women only and, therefore, the sample is not representative of the model cohort as evidence suggests that women are at higher risk of increased mortality due to severe CLBP compared with men (218). Therefore, using mortality risk from this study might overestimate the overall mortality risk.

Based on the previous section, we assume that people with severe CLBP who are older than 75 years have additional risk of mortality compared with younger people (218). In addition, we assume that adults with severe pain have an additional risk of suicide compared with people with less severe pain (220). The transition probabilities after applying all-cause mortality and death from severe pain are summarised in Table 5-4.

Table 5-4 Revised transition probability matrix for intervention arm and standard care where transitions to dead state vary with the age of the patients.

Transition probabilities	PMS	Standard care	Source
Mild to mild	1-(0.04+0.0.01+ P (death, age))	1-(0.10+0+P (death, age))	Net of other probabilities at this node
Mild to moderate	0.04	0.10	(224)
Mild to severe	0.01	0	(224)
Mild to death	P (death, age)	P (death, age)	ONS (234)
Moderate to mild	0.24	0.16	(224)
Moderate to moderate	1-(0.24+0.02+ P (death, age))	1-(0.16+0.06+P(death, age))	Net of other probabilities at this node
Moderate to severe	0.02	0.06	(224)
Moderate to death	P (death, age)	P (death, age)	ONS (234)
Severe to mild	0.46	0.06	(224)
Severe to moderate	0.10	0.06	(224)
Severe to severe	1-(0.46+0.10+Severe to death)	1-(0.06+0.06+Severe to death)	Net of other probabilities at this node
Severe to death	P (death, age) * HR death from disabling pain* HR from suicide	P (death, age) * HR death from disabling pain* HR from suicide	ONS (234),(218),(220)
Death to death	1	1	

5.3.6.4 Utilities, Healthcare Resource Use and Costs

The healthcare resource use and utilities were derived from a UK-based study that aimed to evaluate a stratified primary care intervention compared with usual care (IMPaCT Back trial) (202, 227). The IMPaCT Back trial was conducted in a primary care setting; the inclusion criteria were adult people with CLBP (227). People were excluded if they had serious spinal pathology, such as cancer, infection or inflammation (235). The total number of participants was 922. The mean age of study participants was 53 (SD=15) years and 55% of them were female. Forty one percent had moderate pain, while 37% and 22% had mild and severe pain respectively. The utilities are summarised in Table 5-5.

Table 5-5 Utilities derived from the IMPaCT Back study (202)

Utilities using EQ-5D 3L	(mean, (SD))
Mild pain	0.779 (0.17)
Moderate pain	0.568 (0.28)
Severe pain	0.368 (0.36)

In this study, costs were calculated from the NHS perspective; therefore, only direct costs were included. The direct costs consisted of six main categories, which were GP contact, nurse contact and other healthcare professional contact, including physiotherapy, acupuncture and occupational therapy. Secondary care contacts include NHS consultants, day case procedures and facet joint injections. Diagnostics include X-rays, blood tests, MRI and computerised tomography (CT) scans. The cost for mild, moderate and severe pain was assigned in the PMS and the SC arm. In addition, the PMS arm had an additional initial cost of the PMS visit, which was added to the first cycle. The details of assessing the initial cost of the PMS is discussed later in this section.

The mean healthcare resource use for each state, stratified by type of contact, which was reported in the IMPaCT Back study SC arm (202), was given to experts from our locality. The details of those experts are discussed in section 5.3.6. The original data from the IMPaCT Back study is provided in Appendix J.

The experts were asked about the similarities and differences between healthcare resource use in the study and our practice. Then the experts were asked to assess the data provided and to adjust resource use based on their experience of caring for adults with CLBP in our setting.

The data from the IMPaCT Back study was for healthcare resource use over six months. In order to adjust for our cycle length of 3 months, the mean was divided by 2. In the IMPaCT Back study, 62% of people in the study were suffering from low back pain for more than three months. Evidence from an epidemiological study

conducted in the UK suggested that pain intensity in people with low back pain remains unchanged over 12 months (236). Given that pain intensity tends to remain unchanged over one year, we can assume that the health resource utilisation was consistent over the study period.

In the IMPaCT Back study, the use of prescription medication was reported as the number of people using them and their percentages, instead of means, because of the difficulty in distinguishing between multiple prescriptions. In this model, we inflated the medication cost that was reported in the IMPaCT Back study using inflation indices (237) to reflect current prices. The mean healthcare resource generated from the experts is presented in Table 5-6.

For the initial cost of the PMS, based on expert discussions, we assumed that all people have only one visit to the pain consultant and a follow-up phone call. The estimated cost for the visit and follow-up phone call is £201 (238).

Direct healthcare unit costs were obtained from the following sources: costs of treatment interventions and investigations were derived from NHS reference costs (238) and the costs of healthcare staff from the Personal Social Services Research Unit (PSSRU) (237, 239). All costs were expressed in 2015-2016 pounds sterling. The unit cost and sources are shown in Appendix K.

Table 5-6 Mean CLBP related healthcare resource use (HCRU) per patient and unit costs, by pain intensity level at three months

Healthcare resource	Unit cost	Meeting 1 (two experts)						Meeting 2 (one expert)					
		Mild pain		Moderate pain		Severe pain		Mild pain		Moderate pain		Severe pain	
		Mean HCRU	Cost	Mean HCRU	Cost	Mean HCRU	Cost	Mean HCRU	Cost	Mean HCRU	Cost	Mean HCRU	cost
General Practitioner: surgery consultation	36	0.285	10.26	0.66	23.76	2.5	90.00	0.285	10.26	0.66	23.76	1.5	54.00
General Practitioner: home visit	91.5	0	0.00	0	0.00	0	0.00	0.005	0.46	0	0.00	0.5	45.75
Practice Nurse: surgery consultation	9.30	0.005	0.05	0.065	0.60	0.19	1.77	0	0.00	0	0.00	0	0.00
Practice Nurse: home visit	16.20	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
NHS Consultant	152	0.065	9.88	0.15	22.80	0.265	40.28	0.065	9.88	0.15	22.80	0.265	40.28
NHS hospital admissions	653.00	0.005	3.27	0.01	6.53	0	0.00	0	0.00	0	0.00	0.01	6.53
NHS x-ray	44.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
NHS CT scan	99.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
NHS MRI scan	146.00	0.03	4.38	0.06	8.76	0.05	7.30	0.03	4.38	0.05	7.30	0.06	8.76
NHS blood tests	20.27	0.005	0.10	0.005	0.10	0.01	0.20	0	0.00	0	0.00	0	0.00
NHS epidural injections	730.00	0	0.00	0.005	3.65	0.03	21.90	0	0.00	0.005	3.65	0.03	21.90
NHS physiotherapy	18.00	0.525	9.45	0.725	13.05	0.935	16.83	0.525	9.45	0.725	13.05	0.935	16.83
NHS 'other' healthcare professional*	36.00	0.1	3.60	0.11	3.96	0.315	11.34	0.1	3.60	0.11	3.96	0.315	11.34
Prescribed medication	NA		10.00		21.00		30.00		10.00		21.00		30.00
Total			50.98		104.22		219.62		48.03		95.52		235.39
*Other healthcare professionals include acupuncturists (£52) and occupational therapists (£20)													

In the model, the mean cost generated from the two meetings has been used and the standard deviation was calculated from these two values to generate distribution around the mean. The values are summarised in Table 5-7.

Table 5-7 Mean CLBP related costs per patient, by pain intensity level at three months

Health states	Costs from 1st meeting	Costs from 2nd meeting	Mean (SD) cost
Mild pain	£50.98	£48.03	£49.5 (2)
Moderate pain	£104.22	£95.52	£100 (6)
Severe pain	£219.62	£235.39	£227.62 (11)

5.3.6.5 Assumptions about attrition of effect size

Cognitive behavioural therapy (CBT) is the fundamental component of the biopsychosocial model of pain management. This type of therapy promotes increasing coping skills and improving people's perception towards pain and this model forms the basis of PMS. Theoretically, this suggests that the effect of the intervention is maintained as the patient practices the CBT skills.

An economic evaluation conducted by Norton et al. that aimed to assess the cost effectiveness of CBT in people with CLBP assumed that the CBT effect is reduced by 20% each year (240). The assumption in the study by Norton et al. was based on a systematic review that studied the long term effect of CBT on several psychiatric disorders (241), as little is known about the long term effect of CBT in back pain.

Given the uncertainty around the long term effectiveness of PMS (242), it was assumed that the effect of the service was maintained in the first year. As it did not seem

appropriate to assume that effectiveness was maintained for the lifetime of the patient, the model incorporated an assumption of attrition of effect. Therefore, it was assumed that the effect was relatively reduced by 20%, as reported by Norton et al. (240), and the reduction was maintained for years 2 to 3, based on the findings by Suoyrjo et al. (243). Any remaining effect at year 3 was carried on until the patient exited the model.

A table for the CBT attrition effect was created in TreeAge. This table consists of the total number of cycles and the treatment effect, which was equal to one, except for the 5^{th} cycle till the 12^{th} cycle (year 2 and year 3) when the treatment effect was 0.95. The probabilitiesin the PMS branches were multiplied by the values in this table. For example, if the starting probability in a certain branch was 1, after four cycles (1 year) the probability become 0.80, and then 0.64 in the following year.

5.3.6.6 Subgroup Analysis

Subgroup analysis in economic evaluation (244) is classifying the patients according to their baseline sociodemographic characteristics or clinical characteristics and assessing the benefit they attain from that intervention and/or the cost of providing it.

Several studies showed that greater symptom intensity at baseline is a poor prognostic outcome indicator following the intervention (245-247), however evidence that this effect is directly and solely attributed to the intervention is lacking. Therefore, evidence is needed to demonstrate the cost effectiveness of PMS in CLBP subgroups based on their baseline pain intensity level.

5.3.7 Cost Effectiveness Analysis

The analysis generated the difference in outcomes and costs between PMS and SC and the cost per extra quality-adjusted life-year (QALY) gained by PMS, compared with SC was generated. The incremental cost-effectiveness ratio (ICER), the cost per extra QALY generated by PMS over SC, was calculated using the following equation:

$$ICER = (Cost^{PMS} - Cost^{SC}) / (QALY^{PMS} - QALY^{SC})$$

Deterministic and probabilistic incremental economic analyses were carried out. Where available, data was specified as distributions to fully incorporate the uncertainty around parameter values for probabilistic analysis. The analysis was run with 10000 iterations, using Monte Carlo simulation to obtain point estimates and ranges of QALYs and costs generated by PMS or SC and ICER distributions.

The choices of distributions for particular parameters were based on a general approach by using the distributional form that relates to the estimation of the parameter of interest (207). For utility values, which are bounded to be 0 to 1, the beta distribution was assigned. For costs, gamma distributions were assigned. For multinomial transitions, in the case of transition probability among pain levels, dirichlet distributions were assigned. For hazard ratios, log-normal distributions were assigned (207).

The proportion of ICER estimates in each of the four quadrants of the cost-effectiveness plane were calculated to represent the uncertainty. In a cost effectiveness plane, the south-east (SE) quadrant represents negative costs and positive effects,

which is considered to be dominant or superior. On the other hand, the north-west (NW) quadrant, with positive costs and negative effects, is considered to be dominated or inferior. The north-east (NE) quadrant, with positive costs and effects, and the south-west (SW) quadrant, with negative costs and effects, involve trade-offs. These two quadrants represent the state where the intervention might be cost-effective compared with the comparator, depending upon whether the ICER is higher or lower than the decision maker's willingness to pay (WTP) for an extra QALY.

Cost-effectiveness acceptability curves (CEAC) (197) were constructed to express the probability that PMS is cost-effective as a function of the decision-maker's ceiling ICER (λ) for base case, sensitivity and scenario analyses (248). The currently accepted NICE threshold of £20,000 per QALY gained was used to assess probability of cost-effectiveness (249).

Key model parameters were subject to one-way sensitivity analysis (OSA) to determine the key drivers of the model results. The ranges of input parameters were based on alternative values identified in the literature, the upper and lower limits of confidence intervals of base case estimates, or were arbitrary (employing expert opinions where appropriate). The intervals for deterministic OSA were chosen conservatively, to incorporate maximal level of uncertainty around point estimates. The incremental costs, QALYs and ICERs were calculated for extreme values of the parameters, keeping all other model inputs unchanged. A Tornado diagram was presented for the parameters with the highest impact on the ICER, plotting ranges for ICERs for these parameters in descending order.

Sensitivity analyses were conducted on the following:

1. Varying discount rates from 0-6%.

2. The use of lower and higher costs for each health state based on data provided in NHS reference costs (238).

3. Assuming different costs of intervention including: one visit with no follow up phone call and two visits with one follow up call to assess the impact of the initial intervention cost on the result.

4. The use of utility inputs from another study (STarT Back study (226)) to assess the impact of using different utility values on the result.

Incremental net monetary benefit (INMB) was also used to assess the cost effectiveness of the intervention and was calculated using the following equation:

$$INMB = (QALY^{PMS} - QALY^{sc}) * WTP - (Cost^{PMS} - Cost^{sc}).$$

The INMB approach was used due to challenges associated with incremental cost-effectiveness ratios (ICERs) when the ellipse covers all four quadrants of the cost-effectiveness plane (250, 251). INMB is the difference between the monetary value of the incremental health benefit and the incremental cost of PMS, when compared with SC. A positive INMB indicates that PMS is cost effective compared with SC. The INMB explicitly incorporates the decision maker's WTP and it is easy to interpret the change in the INMB compared with ICER results. A WTP of £20,000 per QALY, as recommended by NICE, was used to generate the INMB.

In the subgroup analysis, the economic evaluation was replicated for each pain intensity level. This was performed assuming all people were at severe, moderate and mild pain at baseline. In addition, the attrition of treatment effect was tested by assuming two possible scenarios, which were no attrition of treatment effect (optimistic) and treatment effect continuing to reduce until all patients exited the model (pessimistic). Finally, the transition probabilties obtained from two months' data were also tested.

5.3.8 Model Validation

The modelling method followed guidelines recommended by the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) criteria (252). The AdViSHE tool assesses the model validity by focusing on four main domains, including conceptual validation, data validation, computerised model validation and operational validation.

The conceptual validation assesses the strength of the theories and the assumptions underpinning model structure and whether the model reflects the real decision problem. The data input validation addresses the accuracy and appropriateness of the data inputs. The computerised model validation ensures that the implemented software programmes, including the mathematical calculations, are performed according to the model specification. Finally, the operational validation assesses the accuracy and applicability of the model outcomes.

In our model, a pharmacist who specialised in pain management and was working in the same practice setting was part of the project team (Roger Knaggs) and provided an

insight about the treatment pathways and outcomes used to assess effectiveness. He also provided input regarding whether the model reflects people attending such services in reality. Secondly, healthcare resource use for people attending PMS were discussed with three GPs who worked closely with the service providers. This was discussed in 5.3.6.

With regard to the computerised model in TreeAge, two experienced health economists provided feedback regarding data inputs, the mathematical aspects of the model and analysis outputs (Georgios Gkountouras and Lukasz Tanajewski). In addition, the final model was presented at two health economics related seminars held at the Universities of Nottingham and Manchester, where a group of health economists provided a detailed review and feedback.

5.4 Results

5.4.1 Base case Analysis

The deterministic cost-effectiveness analysis derived a mean lifetime cost per patient of £3585.87 for the PMS and £3269.93 for SC. The mean number of QALYs generated were 29.83 for the PMS and 29.42 for SC. The incremental cost was £315.93 and the incremental QALY was 0.41. The generated ICER was £761.43 per QALY. The results suggest that PMS is more costly but more effective compared with SC.

In the probabilistic analysis, the mean ICER was £706.98 per QALY gained (2.5th percentile £-3036.54 ;97.5th percentile £2568.714), not dissimilar to the deterministic ICER. In this analysis, as can be seen in Figure 5-4, 27% of the ICER estimates were

in the NE quadrant (PMS more effective, more costly), 24% were in the SE quadrant (PMS more effective, less costly: “dominant”), 10% in the SW quadrant (PMS less effective, less costly) and 39% were in the NW quadrant (PMS less effective, more costly: “dominated”).

Figure 5-5 demonstrates the CEACs. This analysis shows that, at a ceiling willingness to pay of £20,000, the PMS achieves 51% probability of being cost effective. There is a 51% probability that the PMS is both more effective and less costly. The probability of the PMS being cost effective does not increase beyond 51% regardless of how high the decision-maker’s ceiling willingness to pay becomes. The incremental net monetary benefit generated a mean of £7884.07, indicating that the PMS is cost-effective compared with the SC at a WTP of £20,000.

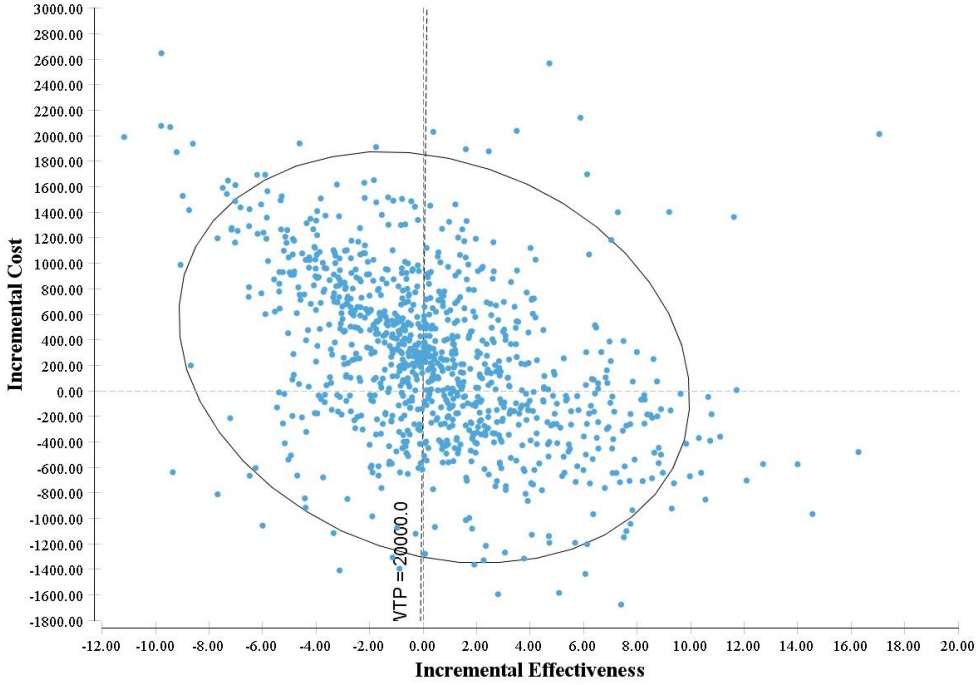


Figure 5-4 Cost-effectiveness plane of probabilistic incremental costs and incremental QALY gain of the PMS versus SC

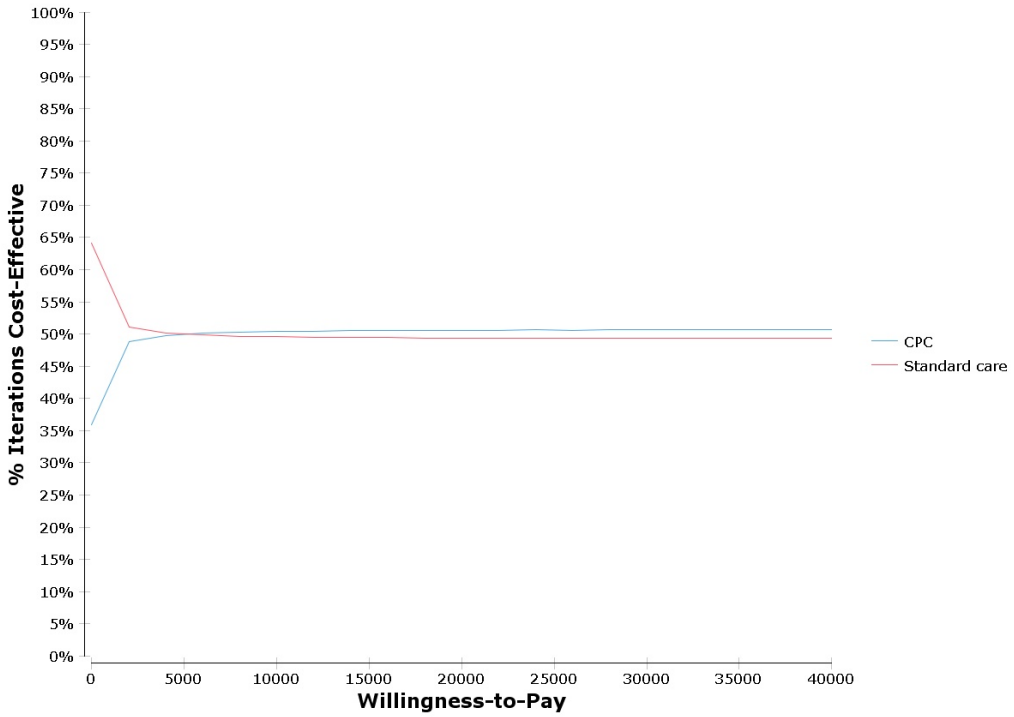


Figure 5-5 Cost effectiveness acceptability curve of PMS versus SC

5.4.2 One-way Sensitivity Analyses

The one-way sensitivity analysis is presented in Figure 5-6 and Table 5-8. The two parameters that had the most impact on the base case ICER were changing the severe pain utility score and increasing the initial cost of the PMS to £426.

Changing the severe pain utility score to the one reported by the STarT Back study (226) significantly reduces the incremental QALY to 0.08. Another parameter that affects the ICER is increasing the initial cost of the PMS to £426, as this increased the incremental cost to £540. A reduction in the incremental QALY and and increase in the incremental cost, respectively, increases the overall ICERs.

The ICERs were not significantly affected by changing the mild and moderate pain utility scores to the STarT Back study (226) and also by using the lower and higher unit costs for healthcare resource use (238).

Table 5-8 One-way sensitivity analysis of the pain management service versus standard care

Parameter (base case value)	Alternative values	Comment / source	ICER (cost\QALY)
Base case			£761.43
Costs (£)			
Cost of mild pain, £49.5	£43	NHS reference costs (238)	685.97
	£53		802.06
Cost of moderate pain, £100	£85		612.40
	£108		1040.85
Cost of severe pain, £227	£200		575.26
	£245		885.54
Cost of intervention, £201 (includes single visit followed by a phone call)	£181	Assuming single visit only	713.22
	£426	Assuming two visits and a phone call	1303.70
Utilities			
Utility of mild pain, 0.779	0.733	STarT Back study (226)	818.43
Utility of moderate pain, 0.568	0.573		839.63
Utility of severe pain, 0.368	0.252		3803.79
Other parameters			
Discount rate, 3.5%	0%	Arbitrary	674.49
	6%		832.32

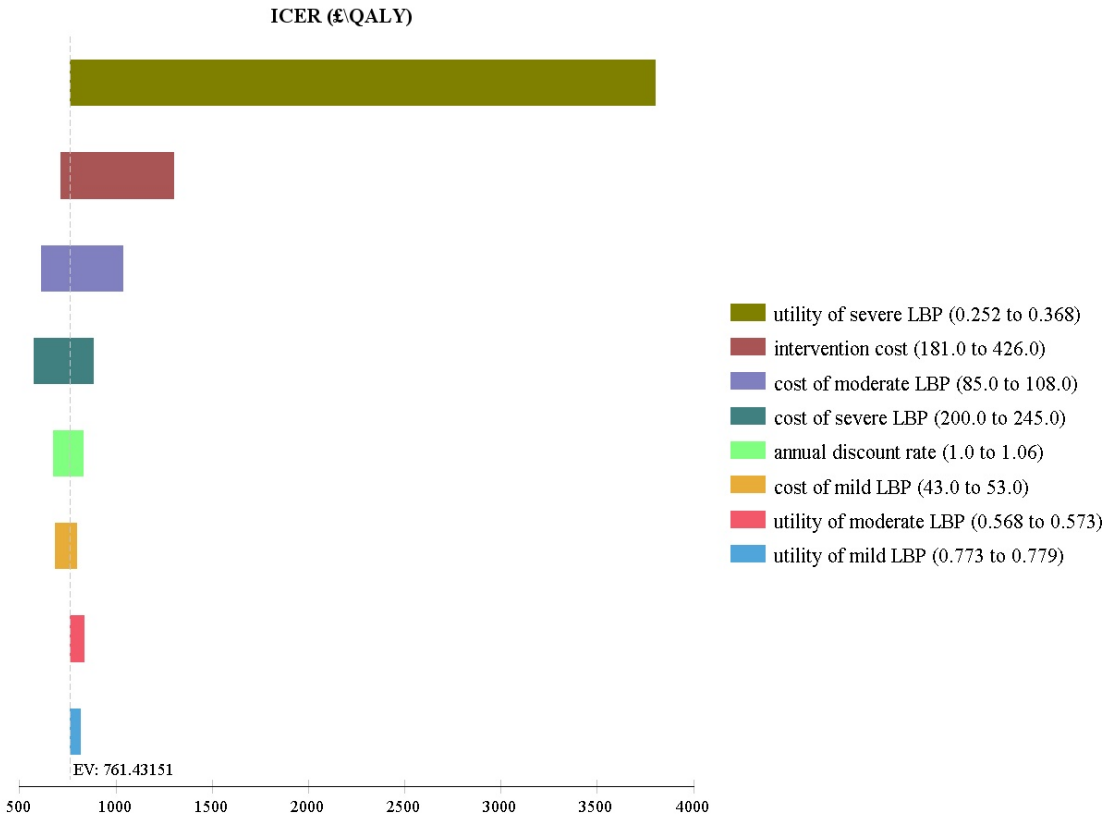


Figure 5-6 Tornado diagram of one-way sensitivity analyses reporting changes in incremental cost effectiveness ratio (ICER)

5.4.3 Scenario Analyses

5.4.3.1 Subgroup by Pain Intensity Level

Within the scenario analysis, PMS was more effective, in terms of incremental utilities, when compared with SC in all subgroups. Regarding the probability of cost effectiveness at a ceiling WTP of £20,000, people with severe pain have a higher probability of cost effectiveness (54%) compared with the base case, whereas people with moderate and mild pain were similar to the base case in terms of the probability of cost effectiveness. The scenario analysis is summarised in Table 5-9.

Table 5-9 ICERs, percentage ICERs in each quadrant and probability of cost effectiveness at λ < £20,000 for base case, scenario analyses by pain intensity level at baseline

Mean ICER (£\QALY)		Incremental Cost	Incremental QALY	% ICER in each quadrant				Prob. CE at WTP £20,000
				NE	SE	SW	NW	
Base case	£706.98	£305.83	0.43	27	24	10	39	51%
Severe pain	£333.78	£207.66	0.62	25	29	10	35	54%
Moderate pain	£801.17	£314.25	0.39	27	23	9	40	51%
Mild pain	£925.07	£332.77	0.36	23	27	10	40	50%

5.4.3.2 Assessing Change in the Treatment Effect over Time

In the base case analysis, the treatment effect relatively reduced by 20% in the second and third year. The remaining effect in the third year was maintained throughout the model. In this section, two scenarios were tested, the optimistic and the pessimistic scenario. The optimistic scenario is that the treatment effect was not reduced (no attrition of effect over time). The pessimistic scenario is that the treatment effect is relatively reduced by 20% starting from the second year until death.

In the optimistic scenario, the probability of PMS being cost effective at a ceiling WTP of £20,000 per extra QALY was 51%, whereas the pessimistic scenario shows less incremental QALYs compared with the base case analysis, which, in turn, signifcantly affects the ICER and the probability of PMS being cost effective was 48%. The scenario analysis is summarised in Table 5-10.

Table 5-10 ICERs, percentage ICERs in each quadrant and probability of cost effectiveness at λ < £20,000 for base case, scenario analyses by changing the treatment effect over time

Mean ICER (£\QALY)		Incremental Cost	Incremental QALY	% ICER in each quadrant				Prob. CE at WTP £20,000
				NE	SE	SW	NW	
Base case PSA (20% relative reduction in treatment effect in year 2 and year 3)								
Base case	£706.98	£305.83	0.43	27	24	10	39	51%
Optimistic scenario (No attrition)								
Optimistic	£636.21	£290.56	0.46	26	24	10	39	51%
Pessimistic scenario (20% relative reduction in treatment effect from year 2 until year 100)								
Pessimistic	£2480.04	£372.18	0.15	27	21	8	42	48%

5.4.3.3 Using two months' data to derive three months' probabilities

In this scenario, two months' data were used to derive the three months' probabilities instead of the twelve months' data that was used in the base case analysis. The results showed that the PMS dominated the SC, which means that the PMS is cheaper and more effective compared with SC. The probability of cost effectiveness using two months' data was 58%. The summary is presented in Table 5-11 .

Table 5-11 ICERs, percentage ICERs in each quadrant and probability of cost effectiveness at λ < £20,000 for base case, scenario analyses by using two months' data to derive probabilities

Mean ICER (£\QALY)		Incremental Cost	Incremental QALY	% ICER in each quadrant				Prob. CE at WTP £20,000
				NE	SE	SW	NW	
Base case PSA (Using twelve months' data to derive three months' probabilities)								
Base case	£706.98	£305.83	0.43	27	24	10	39	51%
Using two months' data to derive three months' probabilities								
Two months' data	£-46.18	£ -23.52	0.51	18	40	10	31	58%

5.5 Discussion

The PMS is more effective and costly compared with SC. The mean ICER was £761 and £706 per QALY gained in the deterministic and probabilistic analyses, respectively. The ICERs were distributed across all four quadrants of the cost effectiveness plane, which demonstrated a high degree of uncertainty. At a ceiling WTP of £20,000 per QALY, PMS reaches a 51% probability of being cost-effective. The probability of PMS being cost effective does not increase beyond 58% in the scenario analysis.

The mean cost per QALY generated suggested that the PMS increased health gain at a cost per QALY well below most accepted cost-effectiveness thresholds for implementation (249). However, the range around this ICER is exceedingly wide, reflecting a great degree of uncertainty. The incremental net monetary benefit value, which is useful when the ICER is associated with a high level of uncertainty, was positive, which indicates that PMS is cost effective compared with SC.

In the one-way sensitivity analysis, the ICERs were affected by the utility score of severe pain and increasing the initial cost of the PMS, while varying the unit cost in each health state or using utility scores for mild and moderate pain from a different study had a negligible effect on results. In the scenario analysis, the incremental QALYs were in favour of the PMS for people with severe pain at baseline. In addition, using the two months' data to derive the probabilties demonstrates that PMS dominated SC and the probability of cost effectiveness was 58%.

The studies reported in Chapter 4 showed inconclusive results about the cost effectiveness of PMS. The PMS was dominant when compared with usual care in the study by Lambeek et al. (20). On the other hand, the PMS was dominated when compared with graded activity plus problem solving (25). Studies comparing PMS with surgery found that PMS is cheaper but less effective (21, 22). In this study, the PMS was more effective and costly compared with SC; however, the results were sensitive to change in the transition probabilities.

Our study has several strengths. Firstly, to our knowledge, this is the first cost-effectiveness study that assesses PMS for CLBP using a decision analysis model over lifetime horizon. Other studies discussed in Chapter 4 included only economic evaluation alongside RCTs. Secondly, in the model we used utilities from two large UK based studies (202, 226) in the base case and sensitivity analysis, which used UK tariffs. The choice of a national tariff is essential to estimate accurately the utilities. Finally, this study assesses the utility gain as an effectiveness measure. Cost utility analyses have an advantage over cost-effectiveness studies using disease specific outcome measures as they allow a comparison between different interventions from disparate therapeutic areas. The use of generic outcomes helps policy makers to allocate resources more efficiently.

However, the decision analysis model also has limitations. Firstly, synthesising evidence from different sources to populate a decision analysis model is associated with uncertainty of the extrapolated clinical and economic input. In addition, there was a lack of certain effectiveness data including the sustainbility of treatment effect over

time and, therefore, several assumptions were made. Probablistic sensitivity analysis and model input validation with clinical and economic experts are the key strategies that were performed in this study to address these uncertainties. The details are discussed below.

Firstly, in order to account for the differences in practice characteristics and service provision, which can affect the cost, we derived our healthcare resource use data from a large UK-based economic evaluation (202) that closely reflected the practice in our setting. The data was also discussed and validated with a group of experts from our locality. However, interviewing GPs from a single locality might limit the generalisability of the cost inputs.

Secondly, this model was based upon a conservative assumption of effect size, in which twelve months' data were used to derive the three months' probabilities. This was chosen to best reflect the treatment effect over the long term and avoiding the overestimated effect of the PMS by using two months' data. In addition, conservative assumptions of PMS effectiveness were made by introducing the attrition of the PMS effect over time; therefore, the ICER in the base case represents a conservative scenario in which the QALYs and cost benefits of replacing SC with PMS are likely to be underestimated. These assumptions were tested in the scenario analyses and the results were sensitive when the probabilities were derived from two months' data.

Apart from the uncertainty associated with the decision analysis model, there were some limitations in the source of the effectiveness data (transition probabilities).

Although transition probabilities are considered to be transferable (182), the intervention assessed by Von Korff et al. (224). is not similar to the intervention delivered by the PMS in Nottingham. The dissimilarity between the two interventions is due to the method of delivery. In the study by Von Korff et al., the intervention was standardised, whereas, in the PMS in Nottingham, the intervention is individually tailored based on the patients' needs. Using the study by Von Korff et al. might lead to underestimating the effectiveness of the service as tailored interventions, which target patients' specific needs, have been shown to be more effective than standardised interventions in other musculoskeletal conditions (253-256).

In addition, several issues from this RCT might explain possible causes for the high uncertainty in the cost effectiveness results. Firstly, the study was powered to detect differences in functional disability using RMDQ (152). In our model, the transition probabilities were based on changes in pain intensity levels. Therefore, the sample size might not adequately detect the changes in pain intensity. Secondly, although the intervention was standardised for all patients, the study reported that some people received extra visits. Given these issues, the difference in pain intensity between the intervention and the control group was modest, as the study was not powered to detect differences in pain intensity. Finally, the number of extra sessions delivered to some people might increase the effect of the intervention.

5.6 Conclusions

This study estimated the economic impact of a community-based PMS, which is known to be effective in reducing pain intensity compared with SC. In the base case analysis, the PMS was more effective and costly compared with SCwith high levels of uncertainty present in the analysis

However, in the scenario analysis, PMS dominates SC when the transition probabilities were derived from two months' data. Scenario analysis also demonstrates that people with severe pain at baseline have more utility gain and less cost compared with the base case analysis. Finally, the utility scores for severe pain and the initial cost of the PMS were shown to have an impact on the ICER in the sensitivity analysis.

Conclusions from this economic evaluation are hampered by the quality of effectiveness data. Therefore, better evidence on the transition probabilities is required. Further work is needed to address the economic impact of targeting people with severe pain at baseline, the effect of the varying utility score of people with severe pain and the initial cost of the PMS.

Chapter 6

Discussion and Conclusion

6.1 Introduction

The research contained in this thesis has made a substantial impact on the knowledge in the field and has identified important factors that need to be considered in designing future research with this group of patients. In this final chapter, a summary of the key findings is made and recommendations and implications are discussed with reference to the main findings and recently published studies related to management of CLBP.

6.2 Summary of Key Research Findings

In the service evaluation study, 32 people were recruited over 10 months. The mean age was 58.8 years, with an equal distribution of both genders. The dropout rates were 21% and 25% over three and six months respectively. Disability was measured using RMDQ (with scores ranging from 0 to 24), where higher scores mean more disability. The mean score at baseline was 13.5 and, after three and six months, the mean was 11.9 and 11.1 respectively. The BPI was used to measure pain intensity and interference. The scores range from 0 to 10, where higher scores mean more pain. The mean score for pain intensity was 5.9 at baseline, followed by a mean of 5.5 and 5.6 at three and six months respectively, whereas pain interference was 5.9 at baseline, followed by a mean of 5.2 at three at six months. As for the EQ5D-3L, higher scores in EQ5D mean better health states. The mean score was 0.38 at baseline and, after three and six months, the scores were 0.46 and 0.40 respectively. The mean number of health visits per patient between baseline and three months was 4, whereas, between four and six months, the mean number of visits per patient was 2.9.

In the systematic review, five studies fulfilled the eligibility criteria. The PMS significantly varied between studies in terms of the number of treatment modalities, intensity and duration. The PMS was compared with either SC, which varied according to the country and the setting, or to two different surgical interventions. In this review, three out of five studies had high risk of bias based on the design of the RCTs. In addition, there were limitations in the statistical and sensitivity analyses in the economic evaluations. Therefore, results from this systematic review need to be interpreted with caution.

In the decision analysis model, the deterministic cost-effectiveness analysis derived a mean lifetime cost per patient of £3585.87 for the PMS and £3269.93 for SC. The mean number of QALYs generated were 29.83 for the PMS and 29.42 for SC. The incremental cost was £315.93 and the incremental QALY was 0.41.

The PMS was more effective and costly compared with SC. The mean ICER was £761.43 and £706.98 per QALY gained in the deterministic and probabilistic analyses, respectively. At a ceiling WTP of £20,000, the PMS reaches a 51% probability of being cost-effective. This suggests that there is 51% probability that the PMS is both more effective and less costly. The incremental net monetary benefit generated a mean of £7884.07, indicating that the PMS is cost-effective compared with the SC at a WTP of £20,000.

In the sensitivity analysis, the results were affected by changing the utility score for severe pain and increasing the cost of the intervention, while varying the unit cost in each health state, or using utilities scores for moderate and mild pain from a different

study, had a negligible effect on results. In the scenario analysis, the incremental cost and QALYs were in favour of the PMS for people with severe pain. The probability of the PMS being cost effective for people with severe pain was 54%, whereas, for people with moderate and mild pain, the probability was similar to the base case. In addition, the sustained reduction in treatment effect reduces the probability of PMS being cost effective (48%). Finally, using the two months' data to generate the transition probabilities demonstrated that PMS dominates the SC and the probability of the PMS being cost effective was 58%

6.3 Strengths and weaknesses

The major strengths in the service evaluation study were the use of validated gold standard health status measures to assess which best reflects the success and acceptability of the service from the patients' perspective. We also obtained detailed information on healthcare resource and medicines use. This is essential to understand the nature and variability of the complex intervention.

From the systematic review, it was clear that the cost effectiveness of PMS is not widely studied. Addressing this question was essential because, firstly, this type of intervention is recommended in national and international guidelines (13, 14) and, secondly, these services are resource intensive (16), and it is documented in the literature that PMS have a moderate effect on clinical outcomes (15). Therefore, cost effectiveness studies are warranted in order to inform policy makers about funding these services.

Finally, this economic evaluation is the first study to assess the life-time effectiveness and cost of PMS on patients with CLBP. All previously published economic evaluations were limited to a duration of two years, which is not sufficient to assess the difference in costs and outcomes. Moreover, the decision analysis model in this thesis has been synthesised using the best-quality evidence available to generate a valid model; this includes using a UK-based study to derive utility scores specific to CLBP patients, cost inputs that were validated with experts from our locality and transition probabilities obtained from patient-level data.

The results of this thesis need to be also cautiously considered in the context of its limitations. With regard to the service evaluation study, there were some limitations. Firstly, the study was performed in a community-based setting, in which the results are not generalisable to other settings. Secondly, the sample size was small; therefore, costs, and utilities data inputs could not be used to populate the decision analysis model. Moreover, there was a lack of a comparative group, due to the difficulty of identifying patients from SC, so there could be no estimates of differences in cost and effectiveness.

In the systematic review, there are several ways in which bias can be seen. Firstly, there was a lack of an agreed definition of the PMS and, therefore, the search was inclusive to all relevant terms. Secondly, language bias (restricting to searching in English) and the risk of publication bias might be introduced, as no attempt was made to locate unpublished studies. Finally, this review is limited by the single assessor who searched and extracted the data. However, the data entry was double checked by

another researcher at the title and abstract screening stage. In addition, the data was extracted using a standardised form approved by the supervisors.

With regard to the decision analysis model, transition probabilities derived from the study by Von Korff et al. might underestimate the effectiveness of the service in Nottingham, as tailored interventions have been shown to be more effective compared with standardised interventions in other musculoskeletal conditions (253-256).

6.4 Thesis contribution

This research aims to evaluate the cost effectiveness of a PMS compared with SC for people with CLBP. A few cost effectiveness studies have been conducted. However, these economic evaluations were alongside RCTs with a short follow up period. In addition, the study that was conducted in the UK was in secondary care and compared the intervention with surgery; therefore, the study did not reflect our population and setting.

To our knowledge, this is the first study that has used a decision analysis model to assess the cost effectiveness of such interventions. This model assesses the long-term cost effectiveness of these services, which was previously unknown. In addition, the systematic review presented in this thesis was the first systematic review that appraised previously published economic evaluations using CHEERS criteria, which is recommended by ISPOR, and the risk of bias in the RCTs, recommended by the CBRG. Finally, this study has assessed the feasibility of evaluating PMS in Nottingham, which was also not previously studied. This service evaluation study was conducted in line with the MRC guidance for assessing complex interventions.

This research highlighted methodological and practical issues that might be encountered when conducting studies for complex interventions. In addition, the systematic review and decision analysis model revealed the major limitations in the previously published economic evaluations and identified possible determinants for the high level of uncertainties reported in the cost effectiveness analysis with recommendations to be addressed in future studies.

6.5 Recommendations

6.6 Recommendations arising from the Service Evaluation Study

6.6.1 Recruitment and Retention

In this study, 32 participants agreed to take part in our study. This number was achieved over 10 months of recruitment. Participants were recruited from two PMS, suggesting that each service recruited around 16 patients. For future studies, the number of services participating in the trial and the recruitment phase needs to be considered in order to achieve the desired sample size.

Loss to follow up is a common challenge in health services research, where data is gathered over longer periods (30, 257). With regard to participant retention, non-responders had high disability and pain intensity/interference compared with complete responders. In addition, the mean age of the non-responders was lower than that of complete responders. A high baseline condition severity (161) and time commitment, especially in people of working age, are factors that affect patient participation in clinical trials (162, 163).

As for retaining study participants, further studies need to engage the people in the study design by having a Patient and Public Involvement (PPI) representative. Evidence suggest that a PPI representative can provide substantial insights into retaining very advanced stages of lung cancer patients by involving patients' carers as a proxy for the patients (258).

6.6.2 Selecting a Comparator Group

There was no comparator group in this study. A comparative evaluation is essential to derive an effect size. Selecting a comparator group for a definitive trial is important as it needs to reflect standard practice. According to the recently published NICE guidelines for CLBP (13), several treatments might be offered, including exercises, pain medicines, cognitive behavioural therapy, a multidisciplinary treatment approach, and other treatment modalities, including radiofrequency denervation. Many treatments recommended in the previous guidelines (1) are no longer recommended in the management of CLBP, including epidural injections, surgery and acupuncture. Given the changes in national guideline recommendations, standard care practice might also change accordingly. Assessing standard care in the setting in which a definitive study is planned is needed when selecting the most appropriate comparator. This can be performed by selecting a study design that can account for such variation.

According to the MRC guidance for evaluating complex interventions (150), patient-level RCTs are usually not feasible due to the possible contamination between the intervention and the standard care arm. Therefore, in order to address the limitations of patient-level RCTs, cluster RCTs might be considered to assess the effectiveness of

a complex intervention, such as a PMS. Cluster RCTs are defined as experiments in which whole social units or clusters of people, rather than independent individuals, are randomly assigned to treatment groups.The advantage of a cluster RCT over a patient-level RCT is that the former can account for the contamination within the cluster. In addition, cluster RCTs are suitable for assessing healthcare services addressing behavioural aspects of patient care (259).

6.6.3 Healthcare Resource Use Data Collection

Although patient diaries were acceptable in terms of clarity, there was an issue that needs to be considered when designing future studies. Some people were not able to specify if the primary care visits to their GP were related to CLBP. Given that this group of people have other comorbidities, frequent visits to GPs for other conditions are expected.

Therefore, in order to address this issue in future studies, a combination of patient self-reported methods, including diaries, and electronic medical records, is suggested. Electronic medical records are useful in documenting the reason for the GP visits and the treatments that were given to the patients. In this study, a comparison between diaries and electronic medical records was planned and approved by the ethics committee; however, given the limitations of time, staffing and funds, we were not able to perform this part of the study (260).

6.6.4 Patient and Public Involvement

In the UK, national regulations require a growing policy effort to involve people and carers in research (261). In this study, a PPI collaborator had been consulted in reviewing the study documents, including questionnaires, patients' information sheets, consent forms and healthcare resource use diaries. The PPI assessment informed the suitability of the study documents, which enriched the quality of the study. For future research, a substantial contribution is needed from PPI collaborators as their role goes beyond reviewing study documents (262). The PPI contribution is essential in the study design and the PPI perspective is needed to address several domains of the research, including the relevance of the research question, advising on suitable recruitment and retention strategies, assessing the burden on study participants and disseminating the research findings to the public.

6.7 Recommendations arising from the Systematic Review

Future studies should aim to clearly describe the intervention in terms of the staff providing the service and the intensity, frequency and duration of each treatment component. In addition, the level of coordination should be clearly described, including the staff member responsible for maintaining the process of delivering the service, the type and frequency of communication between healthcare staff and the setting in which the intervention is delivered.

These issues can be addressed and targeted by using the following solutions (263). Firstly, applying typologies can be used to help in classifying the intervention, based on its common elements, to generate a homogenous group. The Cochrane Effective

Practice and Organisation of Care Review group (EPOC) (264), which aims to conduct systematic reviews of interventions designed to improve healthcare practice and services, has developed typologies to classify these interventions. They also recommend the use of supplementary evidence, which includes trial related data, such as protocols. Access to, or publication of, the trial protocol provides a comprehensive description of the intervention in terms of number and qulification of the staff providing the service, treatment intensity and duration.

In addition to appropriate typologies, future research should also assess the long-term clinical benefit and cost effectiveness of PMS. Limiting variation in the intervention delivery might be required; however, a rigorous study design that increases the internal validity needs to be weighed against the loss of generalisability. Therefore, economic evaluations need to be performed alongside pragmatic cluster RCTs with long term follow up (208). The pragmatic nature of these RCTs retains the concept of randomisation, which minimises the bias; however, it allows for less restrictive criteria that reflect everyday clinical practice and, thus, the results are more generalisability.

6.8 Recommendations arising from Economic Evaluation

6.8.1 The Limitation in the Quality of Evidence Used to Inform the Model

The effectiveness estimates in our model (transition probabilities) were derived from a study that compared an activating intervention with standard care (224). The intervention included four sessions of psychological therapy, combined with physiotherapy, delivered over one month. Several issues from this RCT might explain

possible causes for the high uncertainty in the cost effectiveness results that were discussed in Section 5.5.

6.8.2 Patient Characteristics and Intervention Intensity

CLBP is a heterogeneous condition to manage, due to the lack of specific aetiology and the contribution of psychosocial factors (128). Given these facts, outcomes following PMS is highly variable among people referred to these services (265). This is underpinned by a subgroup analysis performed within a systematic review of the effectiveness of PMS (15). In this systematic review, the severity of baseline symptoms was assessed using a mean pain intensity and disability score. If the mean score for both was 60% or greater of the scale maximum, the study was considered to have "high baseline symptoms intensity". As for the intervention intensity, interventions involving more than 100 hours of face-to-face daily sessions were considered as a "high intensity intervention", whereas studies providing less than 30 hours on a non-daily basis were classified as a "low intensity intervention". Other interventions were classified as "medium intensity interventions" and were excluded from the analysis (130). Unfortunately, subgroup analysis was inconclusive regarding the effect of baseline symptom severity and intervention intensity. This can contribute to the high level of uncertainty in the economic evaluation results.

Generally, subgrouping and risk stratification is one of the research priorities in the CLBP field (266). The recently published NICE guidelines for CLBP recommend using a stratified approach upon the first contact with people with CLBP (13). The guidelines recommend using the STarT Back screening tool (114) developed at Keele

University to classify the people based on their baseline risk score. The tool addresses the modifiable prognostic indicators that are known to affect CLBP treatment within primary care. The tool includes eight domains: referred leg pain, comorbid pain, disability, catastrophising, fear, anxiety and depression and bothersomeness (114). According to the STarT Back tool, people are classified into low, medium and high risk and a matched treatment for each risk group is also described. The NICE guidelines recommend using complex and intensive support, which includes referral to PMS for people with high risk, whereas people with low and medium risk should be offered less intensive treatments (13). However, the quality of evidence supporting the stratification approach was rated as low, due to the lack of blinding to the key confounders that might affect the outcome. In addition, the evidence was based on single studies with a reasonable sample size.

Given the evidence discussed in the previous section, the uncertainty in the cost effectiveness of PMS might arise from the inconclusiveness of the evidence regarding the possible determinants of outcomes following management in these services (15). Moreover, the quality of evidence underpinning the stratified approach in primary care is low (13).

Therefore, other predictor factors that might influence outcomes following the PMS need to be addressed to reduce the uncertainty of the effectiveness of these services. These factors include, but are not limited to, the length of disability, previous surgeries and work-related factors (267). Subgroup analysis based on these predictor factors is warranted in order to identify the groups that might benefit more from this service.

6.8.3 Initial Cost of the PMS

The sensitivity analysis in the model revealed that the initial cost of the PMS is the parameter that highly affects the cost-effectiveness results. Based on the previous section, identifying effectiveness of the intervention, in terms of number of service providers, intensity and duration, will, in turn, help in assessing the initial cost of the PMS. Addressing this major determinant is essential to evaluate the cost effectiveness of the intervention.

However, it should be noted that some interventions are tailored based on the patients' specific needs and, therefore, the initial cost of the PMSwill vary based on the patients' status. Assessing the mean and possible range of intervention cost is critical in quantifying the level of uncertainty in cost data.

6.8.4 Long-term Effectiveness

In our model, the long-term effectiveness of the PMS was based on assumptions as there was no evidence regarding this in relation to the service. Therefore, there is a need to conduct systematic reviews of observational studies that aim to assess the long-term effectiveness of PMS. Conducting such a review will not only provide an insight about the long-term effectiveness of these services, it will also reflect the effectiveness of the intervention on the actual group of people referred to the service in daily practice, due to less restrictive inclusion criteria in this type of study design.

6.9 Implication for Practice and Patients

This research has demonstrated that the PMS might provide some advantages over standard care. However, the high level of uncertainty around the cost-effectiveness estimates prevents being able to draw definitive conclusions for clinical practice.

In this research, it has been demonstrated that people with severe pain at baseline might benefit more from this service compared with people with moderate and mild pain. This is also underpinned by recent NICE guideline recommendations for referring people who are likely to have poor prognostic factors, including high pain intensity at baseline, to these services (13).

Other advantages of using these services have been documented in the literature. Two systematic reviews showed that these services are effective in reducing referral to secondary care by 60% (268). They were also effective in reducing waiting times for orthopaedic consultations (269). This review also revealed that the majority of people with musculoskeletal conditions could be managed without referral to secondary care.

From the clinicians' perspectives (269), being part of a PMS team improves the accuracy of diagnosis and helps in designing a better treatment plan. Furthermore, from the patients' perspectives (269), being treated by such an approach improves their satisfaction, as they are being treated more quickly and efficiently.

6.10 Implications for Policy Makers

Chronic pain treatment is demanding and challenging. PMS, which are based on the modern biopsychosocial model, require an iterative process in development,

evaluation and implementation, based on the MRC guidance (150). This research highlighted areas that need further development in future research. Addressing these issues might help in assessing the cost effectiveness of these services and, therefore, assist policymakers in allocating resources more efficiently.

In order to assess the cost effectiveness of the service in Nottingham, health status measures and healthcare resource use should be routinely collected. Collecting such data for an extended period will provide an estimate of the long-term effect on the PMS. In addition, it will provide a source of transition probabilities, utilities and healthcare resource use that closely reflects our service users.

6.11 Implications for Research

The key challenge in assessing complex interventions, such as PMS, arises because the active components of the intervention are subject to greater variation than in studies assessing pharmacological treatment (270). The MRC guidance for assessing complex interventions recommends using quantitative and qualitative methods in order to comprehensively evaluate such interventions (150). A study conducted by Hadi et al., which aimed to assess pharmacist and nurse led clinics in managing patients with chronic pain, used the mixed method based on the MRC guidance (271). The study desgin was a quasi-experimental study, combined with qualitative interviews. The quasi-experimental design in this study used a single-group pre-test/post-test approach. The author highlighted the impracticality of identifying people receiving SC through GPs, as there is currently no mechanism to identify people receiving this (272). The study design used by Hadi et al. (271) and the

justification of assessing the PMS arm only is similar to the study design and justification used in our study.

The study by Hadi et al. and the studies presented in this thesis were aiming to assess the effectiveness of a complex intervention based on MRC guidance. While Hadi et al. used a qualitative and quantitative study design with a focus on patients' perspective by conducting qualitative interviews, our study addresses the effectiveness and cost effectiveness by using a decision analysis model to inform decision makers about funding such interventions, which all fall under the MRC recommendations, by conducting feasibility studies before designing large RCTs.

When it comes to economic evaluation, specifying the model inputs with sufficient clarity in order to assess the changes in healthcare resource use and outcomes is essential. This can be achieved by selecting an appropriate study design that could accommodate the variable nature of complex interventions without affecting the internal validity of the study.

Trial and model based economic evaluations have their advantages and disadvantages, which have been discussed in this thesis. A study design that can incorporate a pragmatic cluster RCT, where there is likely to be variation in the method of implementing the same intervention, might be needed. The pragmatic feature will increase the external validity of the study and, therefore, the results could be transferable to different population and healthcare systems. Data inputs from this study, including transition probabilities, utilities and costs, were then incorporated in a decision analysis model in order to assess the lifetime cost effectiveness of such an

intervention. Using this study design will overcome the limitations of the trial based economic evaluation by extrapolating cost and outcomes beyond the study follow up period. Uncertainties that arise from the modelling process can be mitigated by appropriate sensitivity analysis and by incorporating clinical and economic experts in the early stages of the model development (252).

Several studies in musculoskeletal conditions, including back pain (273-276) and knee osteoarthritis (277, 278), used economic evaluation alongside pragmatic cluster RCTs to assess various complex interventions, including cognitive patient education, multifaceted guideline implementation, neuroreflexotherapy, minimal psychosocial intervention and integrated rehabilitation. Given that these studies were conducted alongside trials, lifetime cost effectiveness needs to be established.

The study design, which incorporates economic evaluations alongside RCTs combined with decision analysis modelling, has been used in several studies assessing complex interventions for people with chronic conditions, including diabetes, depression, hypertension and COPD (279-283).

Additionally, conducting a qualitative study before, during and after the RCT is essential in assessing several domains that cannot be assessed using a standard quantitative approach (284). Before the RCT, the qualitative studies help in understanding the contextual aspect of the research, intervention components and selecting appropriate outcome measures. During the RCT, qualitative studies identify barriers and facilitators to participation in the study and the feasibility of intervention delivery. Finally, after the RCT, the qualitative approach helps in explaining the

study's findings and variation in the effectiveness within sample subgroups. Finally, patient and public involvement in clinical research is a critical strategy to ensure that the research is examining the questions that are relevant to people who live with a chronic illness condition. In addition, the people's experience is helpful in developing research that might benefit them and their carers.

6.12 Conclusion

Community-based PMS have the potential to improve functional disability and pain interference for people with CLBP in the primary care setting by providing well-timed access to a specialised pain management team, ensuring effective use of pain medicines and streamlining the treatment pathways based on the individual patients' needs. However, the current study design cannot be recommended for a definitive RCT. Substantial methodological amendments are needed to address the best strategies of recruiting and retaining participants and assessing healthcare resource use.

A systematic literature review assessing the economic evaluations of PMS for managing people with CLBP highlighted inconsistent evidence supporting PMS. The cost effectiveness studies included in this systematic review were alongside RCTs with a maximum follow up period of two years. As a result of the limitation of this type of economic evaluation, a decision analysis model was developed in order to assess the life time effectiveness of PMS compared with SC.

The decision analysis model presented in this thesis provides a framework for an iterative economic evaluation and can be updated when further information is available to inform the cost-effectiveness of using PMS for people with CLBP. The PMS is more

effective and costly compared with SC in the base case analysis; however, changing the source of transition probabilities from 12 months to two months demonstrated that PMS dominated SC, providing a potential for PMS to be cost-effective if high quality research is conducted to reduce the uncertainty around transition probabilities. In addition, the economic evaluation suggests that the probability of PMS being cost-effective was higher for people with severe pain at baseline. Finally, the results were also sensitive to change in the utility score of severe pain and the initial cost of the PMS. Therefore, further information, including assessing the utility score for people with severe pain and the initial cost of the PMS, needs to be collected to provide a more robust estimate of the cost-effectiveness of PMS compared with SC. The main results from this thesis highlight the areas requiring improvement through additional feasibility studies before conducting definitive studies of PMS for CLBP.

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Appendices

Appendix A: Baseline questionnaire



Study title

Describing the characteristics, treatment pathways, outcomes and costs of people with nonspecific low back pain managed by community pain clinics in Nottingham and generating an indicative estimate of cost-effectiveness

We are interested in understanding the impact of pain management services on your health outcomes.

Please help us by taking time to complete this questionnaire.

If you have any questions or want to clarify any issues before completing the questionnaire, please contact us using the contact details provided in the information sheet.

The questionnaire will take 10-15 minutes to complete.

Functional disability

This list contains sentences that people have used to describe themselves when they live with back pain. When you read them, you may find that some stand out because they describe you **TODAY**. When you read a sentence that describes you today, put a tick against it. If the sentence does not describe you, then leave the space blank and go on to the next one.

Statement	**Yes**	**No**
1. I stay at home most of the time because of my back.		
2. I change position frequently to try and get my back comfortable.		
3. I walk more slowly than usual because of my back.		
4. Because of my back I am not doing any of the jobs that I usually do around the house.		
5. Because of my back, I use a handrail to get upstairs.		
6. Because of my back, I lie down to rest more often.		
7. Because of my back, I have to hold on to something to get out of an easy chair.		
8. Because of my back, I try to get other people to do things for me.		
9. I get dressed more slowly than usual because of my back.		
10. I only stand for short periods of time because of my back.		
11. Because of my back, I try not to bend or kneel down.		
12. I find it difficult to get out of a chair because of my back.		
13. My back is painful almost all the time.		
14. I find it difficult to turn over in bed because of my back.		
15. My appetite is not very good because of my back pain.		
16. I have trouble putting on my socks (or stockings) because of the pain in my back.		
17. I only walk short distances because of my back.		

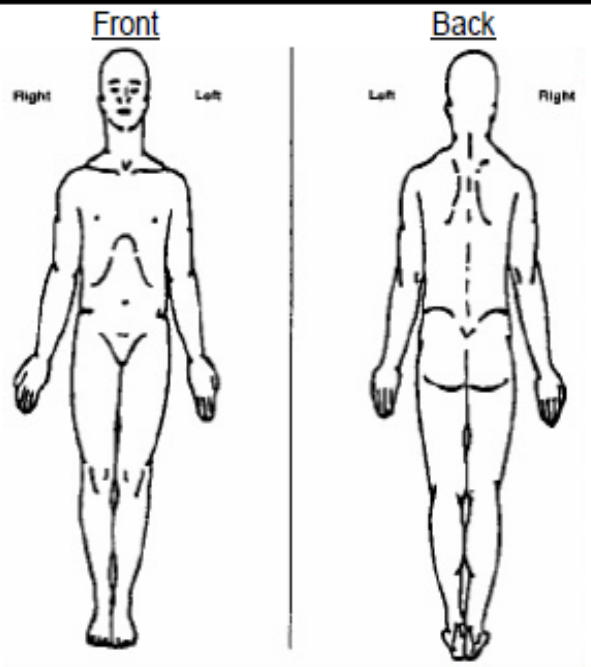
18. I sleep less well because of my back.		
19. Because of my back pain, I get dressed with help from someone else.		
20. I sit down for most of the day because of my back.		
21. I avoid heavy jobs around the house because of my back.		
22. Because of my back pain, I am more irritable and bad tempered with people than usual.		
23. Because of my back, I go upstairs more slowly than usual.		
24. I stay in bed most of the time because of my back.		

Pain assessment

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Your health status today

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

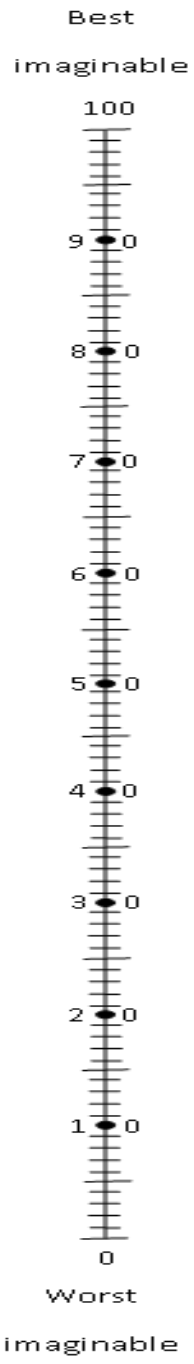
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.





Some questions about you

Are you:

- ○ Male
- ○ Female

How old are you? (Please give your answer in years) ----------

Choose one section from A to E, then tick one box to best describe your ethnic group or background.

A: white	○ English / Welsh / Scottish / Northern Irish / British
	○ Irish
	○ Gypsy or Irish Traveller
	○ Any other White background (please specify)
B: Mixed / multiple ethnic groups	○ White and Black Caribbean
	○ White and Black African
	○ White and Asian
	○ Any other Mixed / multiple ethnic background (please specify)
C: Asian / Asian British	○ Indian
	○ Pakistani
	○ Bangladeshi
	○ Chinese
	○ Any other Asian background (please specify)
D: Black / African / Caribbean / Black British	○ African
	○ Caribbean
	○ Any other Black / African / Caribbean background (please specify)
E: Other ethnic group	○ Arab
	○ Any other ethnic group (please specify)

What is your marital status?

- o Married / Cohabiting
- o Separated / Divorced
- o Widowed
- o Single

How long have you been troubled by back pain? This means when your back pain first ever started.

_____weeks _____ months _____ years

Do you take (prescribed) medicines for your back pain?

o No

o Yes (please specify number of medicines below)

Do you take (over the counter) medicines for your back pain?

o No

o Yes (please specify number of medicines below)

Do you have any other medical conditions?

o No

o Yes (please list your other medical conditions below)

If yes, do you take medicines for these conditions?

o No

o Yes (please specify number of medicines below)

What is the highest qualification you have achieved?

- o CSE /GCSE (or equivalent)
- o O-level (or equivalent)
- o A-level (or equivalent)
- o Degree (or equivalent)
- o Higher degree (or equivalent)
- o Other (Please specify)

Please tick the one option below which you feel best describes you today:

- o Employed fulltime
- o Employed part time
- o Self Employed
- o Unemployed
- o Fulltime student (at least 16 hours/week study)
- o Part time student (less than 16 hours/week study)
- o Unable to work due to long term sickness
- o Homemaker looking after the family or home
- o Unpaid voluntary work
- o Retired
- o Other description (please specify)

Have you been unable to carry out the above activities during the last 6 months due to back problems?

o Yes o No

If yes, for how long?

_____weeks _____ months _____ years

If this survey has raised issues about your treatment in this pain clinic or anything else and you would like to discuss, please contact the researcher or clinic staff and they will be able to take your query.

Thank you for your time

Researcher: Saja Almazrou

Phone: (44) (0) 115 82 32325

Fax: (44) (0) 115 846 6249

Email: paxsa6@exmail.nottingham.ac.uk

Academic supervisors:

Dr Roger Knaggs (Principal Supervisor)

Tel: (44) (0) 115 84 66382

Fax: (44) (0) 115 846 6249

Email: roger.knaggs@nottingham.ac.uk

Prof. Rachel Elliott (co-supervisor)

Tel: (44) (0) 115 8468596

Fax: (44) (0) 115 846 6249

Email: rachel.elliott@nottingham.ac.uk

Appendix B: Ethical approval

NHS
Health Research Authority
NRES Committee East Midlands - Nottingham 1
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839697

24 April 2015

Dr Roger Knaggs
UniversityofNottingham
Schoolofpharmacy
Universitypark
NG7 2RD

Dear Dr Knaggs,

Study title:	**Describing the characteristics, treatment pathways, outcomes and costs of people with nonspecific low back pain managed by community pain clinics in Nottingham and generating an indicative estimate of cost-effectiveness**
REC reference:	**15/EM/0190**
Protocol number:	**15031**
IRAS project ID:	**178806**

The Proportionate Review Sub-committee of the NRES Committee East Midlands - Nottingham 1 reviewed the above application on 24 April 2015.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Ms Rachel Nelson, NRESCommittee.EastMidlands-Nottingham1@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Appendix C: Ethical amendments

NHS
Health Research Authority

East Midlands - Nottingham 1 Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

Tel: 0115 8839269

02 November 2015

Ms Angela Shone
Research and Graduate Services
King's Meadow Campus- Lenton Lane
Nottingham
NG7 2NR

Dear Ms Shone

Study title:	**Describing the characteristics, treatment pathways, outcomes and costs of people with nonspecific low back pain managed by community pain clinics in Nottingham and generating an indicative estimate of cost-effectiveness**
REC reference:	**15/EM/0190**
Protocol number:	**15031**
Amendment number:	**Substantial Amendment SA01 08-10-2015**
IRAS project ID:	**178806**

The above amendment was reviewed on 27 October 2015 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Substantial Amendment SA01 08-10-2015	
Participant information sheet (PIS)	2.0	08 October 2015
Research protocol or project proposal [Describing the management of back pain by community pain clinics.]	2.0	08 October 2015

Appendix D: Consent form

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

CONSENT FORM
(Draft Version 1.0 / Final version 1.0: 25\3\2015)

Describing the characteristics, treatment pathways, outcomes and costs of people with back pain managed by community pain clinics in Nottingham, and generating an indicative estimate of cost-effectiveness

REC ref: ***(to be added after approval given)***

Name of Researcher: Saja Almazrou

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 1.0 dated \ \ for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I agree to take part in the above study. ☐

_____ _____ _____

Name of Participant Date Signature

_____ _____ _____

Name of Person taking consent Date Signature

2 copies: 1 for participant and 1 for the project notes.

Appendix E: Patient information sheet



Participant Information Sheet

(Draft Version 1.1 / Final version 1.0: 27\3\2015)

Describing the characteristics, treatment pathways, outcomes and costs of people with nonspecific low back pain managed by community pain clinics, and generating an indicative estimate of cost-effectiveness

Name of Researcher(s): Saja Almazrou

We would like to invite you to take part in a research study. Before you decide, you need to understand why the research is being done and what it would involve for you. One of our team will go through the Information sheet with you and answer any questions you may have. Please talk to other people about the study if you wish. This information sheet tells you the purpose of this study and what will happen to you if you choose to take part. Please ask us if there is anything that is not clear or if you would like more information about this study.

What is the purpose of the study?

In recent years pain services have been set up in primary care with the aim of providing chronic pain management locally, improving patient's health outcomes, reducing referrals to secondary care and optimizing medication use. In Nottingham, the number of pain management services in the area is limited, leading to poorer care than elsewhere and longer waiting times to receive the optimal health care.

This study aims to describe patients' characteristics, treatment pathways, clinical outcomes and costs of nonspecific low back pain in community-based pain clinics. This will be used to derive estimates of how much the patients benefit from the clinic and what is the cost of managing those patients in community-based pain clinics.

Why have I been invited?

You have been asked to take part in this study because you have been referred to pain management clinic to treat your symptoms. Approximately 80 patients will take part in this study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This would not affect the care you receive at the clinic.

What will happen to me if I take part?

If you fulfil the study criteria, the clinic staff will approach you and ask you if you are interested in taking part. If you initially agree to take part in the study, you will be provided with the study information pack, which includes consent form and the questionnaires that you will be required to fill over the phone during the study. The clinic staff will also collect your contact details to arrange a telephone call with the researcher. You will be able to choose your preferred time slot for the telephone call.

The researcher will contact you within three working days to answer any questions and to confirm your consent to participate. You will be asked to sign the consent form during the phone call and send the form to the researcher by the prepaid envelope provided in the pack. The researcher will sign the form and send a copy back to you.

Also, during the phone call, you will also be asked to complete a short questionnaire provided in the study pack through the phone. The researcher will call you two more times throughout the study to complete the same provided questionnaires. This will happen at 3 months, and 6 months after you received care from the community pain clinics. We will also ask you to keep a diary (provided in the study pack) if you visit any health service facilities e.g. the hospital, your GP practice, etc.

Expenses and payments

You will not be paid for taking part in the study. Travel expenses will be offered for any visits incurred as a result of participation in this study outside your usual care appointments. Please retain your ticket/receipt so that we can reimburse you.

What are the possible disadvantages and risks of taking part?

This study involves you answering questions about your health status by completing questionnaires. We believe that the risks of you taking part in this study are therefore minimal.

What are the possible benefits of taking part?

Unlike the pain management programme, it is less likely that the study will benefit you directly. However, the results from the study may help to improve the future implementation of community pain clinics.

What if there is a problem?

The researcher (Saja Almazrou) will be more than happy to be contacted if you have any questions, concerns or are unhappy with any stages of the study. If you would like to speak to someone other than the researcher, you might wish to contact the academic supervisors, Dr Roger Knaggs or Prof. Rachel Elliott. If you decide to make a formal complaint we would strongly advise you to contact the Patient Advice and Liaison Service (PALS) who will be able to provide you with confidential advice and support and take you through what to do. All contacts can be found at the end of this document.

Will my taking part in the study be kept confidential?

All information collected from the study will be kept confidential. Each participant will be given a study number to ensure anonymity and personal data that identifies them will not be included in reports of publication.

What will happen if I don't want to carry on with the study?

Your taking part in the study is voluntary and you are free to withdraw at any time, without giving any reason, and without usual care being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

The information that you share in the study is confidential and will not be disclosed to your Doctor. However, if an issue arises about your service use that needs further attention we will encourage you to speak to your physician or practice nurse.

What will happen to the results of the research study?

We will share the findings with you if you wish. We can send you a short communication about our findings. This study is a part of PhD project to be submitted to the school of Pharmacy, University of Nottingham as a thesis to get a PhD degree. We will also present

results at conferences and write journal articles so that other people can learn from our study. None will have any of your personal information. Nobody will know that the results are yours.

Who is organising and funding the research?

This research is being organised and funded by the Royal Embassy of Saudi Arabia

Who has reviewed the study?

This study has been reviewed and approved by the Research Ethics Committee. This is an independent organisation which reviews research to ensure that it meets required ethical standards.

Further information and contact details

Researcher: Saja Almazrou
PhD student
Phone: +44(0) 115 82 32325
Email: paxsa6@exmail.nottingham.ac.uk

Academic Supervisors: **Prof. Rachel Elliott**
Lord Trent Professor of Medicines and Health
Tel: (44) (0) 115 8468596
Fax: (44) (0) 115 846 6249
Email: rachel.elliott@nottingham.ac.uk

Dr Roger Knaggs
Associate Professor
Tel: (44) (0) 115 84 66382
Fax: (44) (0) 115 846 6249
Email: roger.knaggs@nottingham.ac.uk

Research team Address:
Division for Social Research in Medicines and Health,
School of Pharmacy, University of Nottingham,
East Drive, University Park, Nottingham, NG7 2RD, U.K.

PALS (Patient Advice and Liaison Service)

Patient Advice and Liaison Service
Moorgreen House
Highbury Hospital
NG6 9DR
Email: PALS@nottshc.nhs.uk

Appendix F: Search strategy

CLBP
coccyx.ti,ab.
coccydynia.ti,ab.
back disorder$.ti,ab.
dorsalgia.ti,ab.
exp Back Pain/
backache.ti,ab.
exp Low Back Pain/
(lumbar adj pain).ti,ab.
back pain.ti,ab.
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

Multidisciplinary pain clinics
multidisciplinar$.tw.
interdisciplinar$.tw.
multiprofessional$.tw.
multimodal$.tw.
patient care team.sh.
exp patient care management/
pain clinics.sh.
(pain clinic$ or pain center$ or pain service$ or pain reliefe unit$ or pain center$).tw.
rehabilitation, vocational.sh.
rehabilitation centers.sh.
rehabilitation clinic$.tw.
rehabilitation.ti,ab.
11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

Economic studies
Economics/
"costs and cost analysis"/
Cost allocation/
Cost-benefit analysis/
Cost control/
Cost savings/
Cost of illness/
Cost sharing/
"deductibles and coinsurance"/
Medical savings accounts/
Health care costs/
Direct service costs/
Drug costs/
Employer health costs/
Hospital costs/
Health expenditures/
Capital expenditures/
Value of life/
exp economics, hospital/
exp economics, medical/
Economics, nursing/
Economics, pharmaceutical/
exp "fees and charges"/
exp budgets/
(low adj cost).mp.
(high adj cost).mp.
(health?care adj cost$).mp.
(fiscal or funding or financial or finance).tw.
(cost adj estimate$).mp.
(cost adj variable).mp.
(unit adj cost$).mp.
(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
Cost effectiveness analysis/
Cost utility analysis/

Combining back pain, multidisciplinary pain clinic and economic studies
24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
10 and 23 and 58

Deduplication and limitation
remove duplicates from 59
limit 60 to humans
limit 61 to English language

Appendix G: CHEERS items

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1, line 1 to 2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 2, line 1 to 23
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	page 3, line 20 to page 4, line 12
		Present the study question and its relevance for health policy or practice decisions.	page 4, line 12 to 18
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 4, line 22 to 23; page 3, line 14 to 19; page 5, line 5 to 9; page 5, line 17 to 22
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 6, line 2 to 8
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 4, line 15 to 18; page 9, line 11 to 13; page 33, table 3
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page 6, line 9 to 16; page 18, line 13 to page 19, line 9

Section/item	Item No	Recommendation	Reported on page No/ line No
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 4, line 21 to 22; page 8, line 3 to page 9, line 10; page 21, line 2 to 4
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 9, line 17 to 18
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page 4, line 15 to 18; page 6, line 23 to 24; page 9, line 23 to 24; page 11, line 9 to 11
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	page 6, line 20 to page 7, line 6; page 7, line 11 to 14; page 31, table 1; page 32, table 2; page 9, line 23 to page 10, line 6; page 35, table 5
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	not applicable
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	

Section/item	Item No	Recommendation	Reported on page No/ line No
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page 8, line 1 to page 9, line 16; page 31, table 1; page 33, table 3
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page 33, table 3; page 9, line 16 to 17
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page 4, line 21 to 22; page 34, table 4; figure 1, figure2, and figure 3
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 6, line 9 to 16; page 6, line 20 to page 7, line 9; page 7, line 15 to 24; page 9, line 13 to 16; page 35, table 7
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	page 11, line 14 to page 12, line 10; page 35, table 7
Results			

Section/item	Item No	Recommendation	Reported on page No/ line No
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	page 7, line 9 to 14; page 8, line 1 to page 9, line 13; page 31, table 1; page 32, table 2; page 33, table 3; page 34, table 4; page 9, line 23 to page 10, line 6; page 35, table 5; page 35, table 7; page 36, table 8
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	page 12, line 17 to page 13, line 24; page 36, table 9; figure 4
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	page 14, line 1 to 14; figure 5
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability	not applicable

Section/item	Item No	Recommendation	Reported on page No/ line No
		in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	page 8, line 27 to page 12, line 27
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Information provided via the submission system
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Information provided via the submission system

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

Appendix H: List of excluded studies and reasons for exclusion

Study	Reason for exclusion
Whitehurst 2007 (285)	Acute back pain
Strong 2006 (286)	Single intervention
Fritzell 2004 (287)	Not multidisciplinary intervention
Jensen 2013 (140)	Mixed conditions
Rogerson 2009 (288)	Acute LBP
Jensen 2009 (289)	Mixed conditions
Sogaard 2008 (290)	Post-surgery
Goossens 1998 (291)	Single intervention
Hill 1996 (292)	Partial economic evaluation
Kominski 2005 (293)	Partial economic evaluation
Loisel 2002 (294)	Sub-acute pain
Berenguera 2011 (23), Lambeek 2007 (295), van der Roer 2004 (296)	Protocols
Weh 2011 (297)	Abstract
Henchoz 2010 (298)	Different intervention
Uhlig 2003 (299)	Review

Appendix I: National life tables (2013-2015)

Age	Mortality rate	
	Males	Females
41	0.001659	0.000949
42	0.001777	0.001076
43	0.001854	0.001161
44	0.002066	0.001277
45	0.002246	0.001394
46	0.002378	0.001479
47	0.002560	0.001611
48	0.002688	0.001747
49	0.003004	0.001902
50	0.003221	0.002163
51	0.003463	0.002308
52	0.003701	0.002526
53	0.004033	0.002795
54	0.004489	0.002995
55	0.004868	0.003362
56	0.005348	0.003623
57	0.005981	0.004000
58	0.006580	0.004241
59	0.007286	0.004695
60	0.008077	0.005234
61	0.008721	0.005719
62	0.009593	0.006210
63	0.010487	0.006801
64	0.011469	0.007308
65	0.012331	0.007988
66	0.013051	0.008481
67	0.014401	0.009481
68	0.015802	0.010672
69	0.017813	0.011647
70	0.019495	0.013015

Age	Mortality rate	
	Males	Females
71	0.021560	0.014339
72	0.024752	0.016116
73	0.026989	0.018277
74	0.030317	0.020312
75	0.033059	0.022436
76	0.036408	0.025071
77	0.040036	0.027839
78	0.044791	0.030916
79	0.049452	0.035425
80	0.056456	0.040553
81	0.062516	0.045640
82	0.071221	0.051959
83	0.079521	0.058719
84	0.088508	0.067531
85	0.100377	0.076003
86	0.111092	0.085465
87	0.123569	0.097278
88	0.138366	0.108463
89	0.152513	0.122870
90	0.168240	0.138451
91	0.183834	0.152324
92	0.205371	0.170413
93	0.227692	0.191161
94	0.241665	0.209367
95	0.264271	0.226339
96	0.278605	0.244355
97	0.305800	0.268462
98	0.334140	0.292079
99	0.351375	0.317580
100	0.381118	0.335497

*Source: National life tables based on data for the years 2014-2016, United Kingdom (234)

Appendix J: CLBP related resource use per patient, by pain level, for participants providing data at six months from the IMPaCT Back trial [a]

Healthcare resource	Mild pain	Moderate pain	Severe pain
General Practitioner: surgery consultation	0.57 (0.9)	1.32 (1.6)	1.95 (2.5)
General Practitioner: home visit	0.01(0.1)	0.00 (-)	0.00 (-)
Practice Nurse: surgery consultation	0.01 (0.1)	0.13 (0.5)	0.38 (1.0)
Practice Nurse: home visit	0.00 (-)	0.00 (-)	0.02 (0.1)
NHS Consultant	0.13 (0.4)	0.30 (0.8)	0.53 (1.0)
NHS hospital admissions	0.01 (0.1)	0.02 (0.1)	0.00 (-)
NHS x-ray	0.06 (0.2)	0.12 (0.3)	0.31 (0.6)
NHS CT scan	0.00 (-)	0.01 (0.1)	0.00 (-)
NHS MRI scan	0.06 (0.2)	0.12 (0.3)	0.10 (0.3)
NHS blood tests	0.02 (0.2)	0.01 (0.1)	0.02 (0.1)
NHS epidural injections	0.0 (-)	0.01 (0.1)	0.06 (0.2)
NHS physiotherapy	1.05 (2.3)	1.45 (0.8)	1.87 (2.8)
NHS 'other' healthcare professional [b]	0.20 (1.8)	0.22 (1.0)	0.63 (1.9)
Prescribed medication [c]	33 (41)	61 (59)	33 (69)
'Over-the-counter' treatments [c]	36 (44)	55 (53)	29 (60)

a Values are mean and SD unless stated otherwise
b Comprising acupuncture, osteopathy and 'other' healthcare professionals.
c The number (percentage) of participants reporting usage within the out-of-pocket and prescribed medication categories are given, instead of mean (SD) items/prescriptions, because of the inability to distinguish between multiple purchases and/or prescriptions.

Appendix K: Health services unit cost included in the model

Health service		Cost	Reference
GP	GP surgery consultation	£36	(section 10.3b),PSSRU 2016 (237) (contact for 9.2 minutes from PSSRU 2016)
	GP Home visit	£91.5	(section 10.3b),PSSRU 2016(237)(contact for 23.4 minutes from PSSRU 2010)
Nurse	Nurse visit	£9.30	(section 10.2),PSSRU 2016(237)(contact for 15.5 minutes from PSSRU 2014)
	Nurse Home visit	£16.2	(section 10.2),PSSRU 2016(237)(contact for 27 minutes from PSSRU 2010
Other HCP	Occupational therapist	£20	(section 11.5), PSSRU 2016(237)(contact for 30 minutes from PSSRU 2010)
	Physiotherapist	£18*	(section 9.1),PSSRU 2014(239)(contact for 30 minutes from PSSRU 2010)
	Acupuncturist	£52	Currency code: AB23Z, NHS reference cost 15-16 (238)
PMS	Consultant- first visit	£181	Currency code: WF02B,NHS reference cost 15-16 (238)
	Consultant-Follow up visit	£225	Currency code: WF02A, NHS reference cost 15-16 (238)
	Consultant-telephone follow up	£20	Currency code: WF02C, NHS reference cost 15-16 (238)
Secondary care	MRI scan (for one area)	£146	Currency code: RD01A, NHS reference cost 15-16 (238)
	CT scan (for one area)	£99	Currency code: RD20A, NHS reference cost 15-16 (238)
	X-Ray (for one area)	£44*	Castelnuovo et al (300)
	Blood test	£20*	Wright et al (301)
	Facet joint injection	£730	Currency code: AB16Z, NHS reference cost 15-16 (238)
	Consultant (spinal surgeon)	£152	Currency code: WF01B, NHS reference cost 15-16 (238)
	NHS day case	£653	Currency code: HC32K, NHS reference cost 15-16 (238)
Medication	Mild pain	£10*	IMPaCT Back study
	Moderate pain	£21*	IMPaCT Back study
	Severe pain	£30*	IMPaCT Back study
*cost inflated to current year (2015-2016) using health service cost index			