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A programme of feasibility studies to develop a randomised controlled trial to assess pain management services for people with fibromyalgia or chronic widespread pain

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Abstract

Background

Fibromyalgia (FM) and chronic widespread pain (CWP) are highly prevalent chronic painful conditions that have substantial impact on patients, health care systems, and society. Diagnosis is complex and management strategies are associated with various levels of evidence for effectiveness and cost-effectiveness. Pain management services (PMSs) have been shown to be effective in some settings and are therefore recommended by clinical practice guidelines as a rational treatment. As these services are resource intensive, evidence is needed to demonstrate their cost-effectiveness.

Quality-adjusted life-years (QALYs) are commonly used as an outcome for the economic evaluation of health interventions. To perform an economic evaluation, mapping from a disease-specific measure onto a generic preference-based measure is essential when utility values of health states are not available in the same sample. In the field of FM/CWP, mapping studies that have estimated the EuroQoL 5-dimensional 3-level instrument (EQ-5D-3L) from the Revised Fibromyalgia Impact Questionnaire (FIQR) are lacking.

Aims

The aim of the research was to conduct a programme of feasibility work in preparation for the conduct of a definitive randomised controlled trial (RCT) of PMSs in managing people with fibromyalgia or chronic widespread pain, compared with standard care (SC). The programme included a systematic review, a feasibility observational study, an economic modelling, and a statistical mapping of FIQR to EQ-5D-3L.

Methods

The study followed the Medical Research Council (MRC) recommendations for evaluation of complex interventions through an iterative process of observation work before evaluation by large scale studies. Therefore, this work comprised four phases. Firstly, a systematic review was performed, using standard methods of systematic review along with quality and reporting criteria for published economic evaluation studies of PMSs in people with FM/CWP. An electronic search was performed in clinical and economic databases, from their inception to April 2016. Full economic evaluations undertaken from any perspective were included. The Cochrane Risk of Bias tool and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist were used to assess the methodological quality.

Secondly, a prospective observational multicentre study, using patient-level data was conducted among newly referred adults with FM/CWP (≥18 years-old) at two community-based PMSs in Nottingham. The feasibility of the study and recruitment, retention and follow-up rates were assessed. Participants provided details of clinical outcomes and health resource-use, using a postal questionnaire and diaries, at baseline and then three and six months after recruitment. Outcome measures were the FIQR, the Brief Pain Inventory (BPI), and the EQ-5D-3L.

Thirdly, data from the observational study, systematic review and secondary data sources were then integrated in a de novo Markov decision analytic model to assess the cost-effectiveness of PMSs compared with SC. Data included transition probabilities, utilities, healthcare resource use and their costing tariff. Costs per extra QALY were calculated from the perspective of National Health Services (NHS) England, using a lifetime horizon. For validating the decision analytic model, the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) criteria were followed.

Finally, access to an anonymised dataset of 160 Spanish adults (≥18 years-old) with a confirmed diagnosis of FM, according to the American College of Rheumatology

(ACR) 1990 criteria, was obtained from a researcher, to perform the mapping from the FIQR to the EQ-5D-3L. The econometric models investigated were ordinary least square (OLS), censored least absolute deviations (CLAD) and multinomial logistic (MNL) models. The choice of model was based on the 'Best' performance, which was defined as: the lowest absolute difference (AD), mean absolute error (MAE), and root mean square error (RMSE), and the highest R^2 statistics.

Results

In the systematic review, six economic evaluation studies of PMSs in people with FM/CWP were identified. However, due to methodological weakness and variability, the review was unable to draw a firm conclusion about the cost-effectiveness. In addition, all identified studies were performed alongside randomised controlled studies (RCTs) with a short follow-up period. As FM/CWP are chronic diseases, the effectiveness and cost-effectiveness over longer periods of time need further investigation, and it is likely that this will require the use of economic evaluation modelling approaches.

Recruitment to the observational study was a significant challenge. Despite modifications to the study protocol to enhance recruitment and retention, only 14 participants were identified, of whom 10 were recruited and eight completed the study (July 2015-September 2016). Hence, the effectiveness and healthcare resource use data were affected by the small sample size

Following the integration of data from the feasibility work and published studies, PMS generated a mean of 15.2 (2.5% percentile -1.7; 97.5% percentile 33) more QALYs per patient, at a mean reduced cost of -£10453 and -£11148.8 (2.5% percentile -£31420.2; 97.5% percentile £3494.5) for deterministic and probabilistic analysis, respectively. PMS has a 97% probability of cost-effectiveness compared with SC at a willingness-to-pay of £20000 per QALY. Sensitivity analysis demonstrated that targeting each disease severity with PMS has a probability over 0.96 of cost-effectiveness compared with SC, at a willingness-to-pay of £20000 per QALY.

In the mapping sample, it was possible to map from the FIQR to the EQ-5D-3L. The predicted mean utilities in all OLS models were identical (up to four decimals) to the observed means. Among the ten specifications used, the best performing model was an OLS model, which included the FIQR (collapsed items in a discrete form), age, and educational level as independent variables in the regression. This model produced lowest errors (AD = 0.0000; MAE = 0.1279; MSE = 0.1576; R2= 0.4675) compared with the more advanced CLAD and MNL models.

Conclusions

The programme of feasibility work performed in this thesis found that due to the low sample size in the feasibility observational study, it has been concluded that it is not feasible to perform a future RCT to evaluate the cost-effectiveness of PMS for people with FM/CWP. However, this study has highlighted key methodological issues which should be taken into consideration in future studies. Moreover, the systematic review highlighted has key design areas that researchers need to consider when conducting economic evaluations, including following standard design guidelines. The indicative economic evaluation of PMS for people with FM/CWP suggested that PMS can lead to a significant health gain and cost savings to the NHS. Finally, it was found that mapping from the FIQR to the EQ-5D-3L is possible. The OLS was the best performing model, which predicted the mean tariff score of the EQ-5D-3L with an accuracy of up to four decimal places. Findings from the statistical mapping will enable future researchers to perform economic evaluations in the absence of EQ-5D-3L data from RCTs of FM/CWP.

Publications

AlAujan, S., R. Elliott and R. Knaggs (2015) "Systematic Review of Economic Evaluations in Multidisciplinary Pain Management Services for Managing People with Fibromyalgia or Chronic Widespread Pain." Value in Health. 18(7): A660.

Abstract presented as a poster at the18th Annual European Congress of International Society for Pharmacoeconomics and Outcomes Research (ISPOR) in Milan, November 2015.

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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AlAujan S., Elliott R., Knaggs R., Luciano J. (2017) "Statistical Mapping of Utility Scores from The Revised Fibromyalgia Impact Questionnaire." Value in Health. 2017; 20(5): A330.

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Table of contents

Abstract i
Publications v
Acknowledgment.....vi
Table of contents viii
List of tables xi
List of figures xiv
List of abbreviations.....xv
Chapter 1: Thesis introduction 1
1.1 Introduction to thesis.....2
1.2 Structure of the thesis.....3
Chapter 2: Literature review, aims and objectives 7
2.1 Introduction to the literature review 8
2.2 Fibromyalgia and chronic widespread pain 8
2.3 Pain management services in managing FM/CWP 32
2.4 Summary of the literature review.....38
2.5 Study Justification.....38
2.6 Methodological Justification.....40
2.7 Thesis aims and objectives.....43
Chapter 3: Systematic review of economic evaluation studies of pain management services for managing people with fibromyalgia or chronic widespread pain.....46
3.1 Introduction.....47
3.2 Objectives 47
3.3 Methods.....47
3.4 Results.....52
3.5 Discussion 69
3.6 Conclusion 72
Chapter 4: Patient characteristics, treatment pathways, effectiveness, and healthcare resource use of PMSs in Nottingham for patients with FM/CWP: a feasibility study 73

4.1 Introduction 74
4.2 Objectives 74
4.3 Methods 75
4.5 Results 89
4.6 Discussion 109
4.7 Conclusion 115
Chapter 5: The indicative cost-effectiveness of PMSs compared with standard care in the management of FM/CWP- a Markov decision analytic model 117
5.1 Introduction 118
5.2 Objectives 118
5.3 Methods 119
5.4 Results 154
5.5 Discussion 167
5.6 Conclusion 171
Chapter 6: Statistical mapping of utility scores (EQ-5D-3L) from the revised fibromyalgia impact questionnaire (FIQR) 172
6.1 Introduction 173
6.2 Recommendations for the use of mapping methods 173
6.3 Summary of recommendations in the literature 182
6.4 Objectives 183
6.5 Methods 183
6.6 Results 190
6.7 Discussion 215
6.8 Conclusion 222
Chapter 7. Thesis discussion 223
7.1 Introduction 224
7.2 Summary of key findings 224
7.2 Strength and weakness 226
7.3 Implications 229
7.5 Future recommendations 233
7.6 Conclusions 238
References 239

Appendices 256

Appendix 1. Study protocol paper 256

Appendix 2. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia.....264

Appendix 3. The Widespread Pain Index and the Symptoms severity items in the 2010, 2011, and 2016 ACR criteria 265

Appendix 4. Classification scheme for bias assessment according to The Cochrane Review Group 266

Appendix 5. CHEERS checklist - Items to include when reporting economic evaluations of health interventions 268

Appendix 6. Search strategies and results.....270

Appendix 7. Patient information sheet.....272

Appendix 8. Consent form.....275

Appendix 9. Patients' quationnaires 276

Appendix 10. Ethical approval from NRES Committee North East – York 287

Appendix 11. Ethical approval from Research and Development Management Nottinghamshire Healthcare NHS foundation Trust.....289

Appendix 12. Good clinical practice certificate.....290

Appendix 13. Ethical approval for the amendments from NRES Committee North East – York 291

Appendix 14. Ethical approval for the amendments from Research and Development Management Nottinghamshire Healthcare NHS foundation Trust 292

Appendix 15. Health care services cost 293

Appendix 16. Long term effectiveness studies of PMS in FM/CWP 294

Appendix 17. Testing the assumptions for OLS estimation 296

List of tables

Table 1. Summary of ACR diagnostic strategies 14
Table 2. OMERACT's recommended domains in FM/CWP and outcome measures with respective psychometric properties 18
Table 3. Non- pharmacological and pharmacological management of FM/CWP 24
Table 4. Estimates of standardised mean difference (SMD) with 95% confidence interval for pharmacological and non-pharmacological interventions in FM/CWP symptoms 26
Table 5. Characteristics of included studies 55
Table 6. Results of methodological quality assessment using CHEERS criteria 59
Table 7. Components of each intervention in the included studies 61
Table 8. Results of incremental cost, QALY and ICER presented in the included studies 67
Table 9. A summary of measures used and their main features 79
Table 10. A summary of method and time of data collection 85
Table 11. Baseline characteristics of non-completers compared to completers 93
Table 12. Baseline socio-demographic and clinical characteristic of FM/CWP patients during study period 94
Table 13. FM/CWP medicines, comorbidities, and medicines for comorbidities for the ten patients 96
Table 14. Comparison of physical functioning of SIQR at baseline, three months and six months post-referral 98
Table 15. Comparison of overall impact domain at baseline, three months and six months post-referral 99
Table 16. Comparison of symptom severity domain of SIQR at baseline, three months and six months post-referral 101
Table 17. Comparison of total SIQR summary score at baseline, three months and six months post-referral 102

Table 18. Comparison of symptom severity domain of BPI at baseline, three months and six months post-referral 103
Table 19. Comparison of pain interference domain of BPI at baseline, three months and six months post-referral 105
Table 20. Comparison of quality of life at baseline, three months and six months post-referral 106
Table 21. Utilisation pattern of medicines in FM/CWP patients attending PMS during study period 107
Table 22. Two- and twelve- months transition probabilities for FM/CWP patients receiving PMS and SC in Luciano et al study (128). 131
Table 23. Calculated three-month transition probabilities from two- and twelve-months probabilities for the PMS and SC pathways 133
Table 24. Age-adjusted all-cause mortality rates in the United Kingdom 134
Table 25. Revised transition probability matrix for PMS and SC where transitions to dead state vary with the age of the patients. 136
Table 26. Elicited mean (SD) healthcare resource use per patient by FIQR severity for participants with fibromyalgia in three months from different countries 138
Table 27. Estimated health care resource use and cost for three-month period of chronic management, stratified by FM intensity levels 140
Table 28. EQ-5D-3L utilities value for fibromyalgia 142
Table 29. Summary of all Markov model inputs 147
Table 30. Summary of ICERs generated for base-case deterministic and probabilistic incremental analysis of PMS versus SC 155
Table 31. One-way sensitivity analysis for cost-effectiveness of PMS compared with SC in FM\CWP patients 159
Table 32. Mean and incremental cost, and QALYs, ICERs, percentage of ICERs in each quadrant of the cost-effectiveness plane, and probability of cost-effectiveness at WTP of £20000 for deterministic, PSA, and scenario analysis 162
Table 33. Recommended alternative specification of mapping function 179
Table 34. Selected regression model specifications 187
Table 35. Socio-demographic and clinical characteristics 191

Table 36. Results of regression model specifications 194
Table 37. Primary model choice by overall ranked score of performance across regression models 196
Table 38. Mean Absolute Error and Root Mean Squared Error of best model (model 6), by EQ-5D Index Range 197
Table 39. Independent variable coefficients by regression model with EQ-5D-3L as dependent variable 200
Table 40. Log odds from multinomial logistic regression using EQ-5D-3L domain scores and FIQR total and domain scores* 206
Table 41. Coefficients and summary statistics for the best performing model 213

List of figures

Figure 1. Flow diagram for included and excluded studies 53
Figure 2. Summary of risk of bias using the Cochrane Back Review Group Criteria .. 58
Figure 3. Flow diagram of recruited participant with FM/CWP 92
Figure 4. Stratification of patients based on FM/CWP duration in years 95
Figure 5. Healthcare resource use per patient during the study period 108
Figure 6. Pain management service pathway, based on the interviews with GPs 122
Figure 7. Standard care pathway, based on the interviews with GPs 123
Figure 8. Model structure, health stated based on the FIQR severity level 127
Figure 9. An example for the application of attrition of PMS effect in the base case analysis 144
Figure 10. Diagram representing the attrition of PMS effect in the base case, optimistic and pessimistic scenarios 151
Figure 11. Incremental economic analysis of PMS intervention versus SC 157
Figure 12. Cost effectiveness acceptability curve of PMS intervention versus SC 157
Figure 13. Tornado diagram demonstrating one-way sensitivity analysis of each variable in the model 160
Figure 14. Distribution of FIQR total score and EQ-5D-3L utility index 192

List of abbreviations

ACPR Augmented Component-Plus-Residual plot
ACR the American College of Rheumatology
AD absolute difference
AdViSHE the Validation Status of Health-Economic decision models criteria
APS American Pain Society
AWMF Association of the Scientific Medical Societies in Germany
BPI Brief Pain Inventory
BPS British Pain Society
CBT Cognitive behavioural therapy
CCG Clinical commissioning group
CEAC cost-effectiveness acceptability curve
CENTRAL Cochrane Central Register of Controlled Trials
CHEERS Consolidated Health Economic Evaluation Reporting Standards
CLAD censored least absolute difference
CMO Chief Medical Officer
CPRD Clinical Practice Research Datalink
CPS Canadian Pain Society
CSPMS core standards for pain management services in the UK
CWP chronic widespread pain
DES Discrete event simulation
EQ-5D EuroQol- 5 Dimension
EULAR the European League Against Rheumatism
FDA the US Food and Drug Administration
FIQ the Fibromyalgia Impact Questionnaire
FIQR the Revised Fibromyalgia Impact Questionnaire
FM Fibromyalgia
FMA the Fibromyalgia Association
GPs general practitioners
HADS The Hospital Anxiety and Depression Scale
HCHS the Hospital and Community Health Services
HCP health care practitioner
HEED the Health Economic Evaluation Database
HRQoL Health-related quality of life
HRU healthcare resource use
HTA Heath Technology Assessment
HTAs health technology appraisals
HUI health utility index

IASP International Association for the Study of Pain
ICER the incremental cost-effectiveness ratio
IMMPACT The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
INMB incremental net monetary benefit
IQR interquartile
ISPOR International Society for Pharmacoeconomics and Outcomes Research
LOCF last observation carried forward
MAE mean absolute error
MASQ Multiple Abilities Self-report Questionnaire
MFI-20 Multidimensional Fatigue Inventory
MNL multinomial logistic
MOS Medical Outcomes Study
MPQ McGill pain questionnaire
MRC Medical Research Council
MRI magnetic resonance imaging
NE North-east quadrant
NETSCC National Institute for Health Research Evaluation, Trials and Studies Coordination Centre
NHS EED NHS Economic Evaluation Database
NHS National Health Service
NICE The National Institute for Health and Care Excellence
NRS Numeric pain rating scale
NSAIDs Non-steroidal anti-inflammatory drugs
NW North-west quadrant
OLS Ordinary Least Square
OMERACT the Outcome Measures in Rheumatoid Arthritis Clinical Trials
ONS Office of National Statistics
OSA One way sensitivity analysis
PMSs Pain management services
PPI patient and public involvement
PSSRU Personal Social Services Research Unit
QALYs quality-adjusted life-years
RA rheumatoid arthritis
RCGP Royal College of General Practitioners
RCT Randomised controlled trial
RMSE root mean square error
ROB Cochrane Risk of Bias tool
SC Standard care
SE South-east quadrant
SF-36 Medical Outcomes Survey Short Form

SF-6D the six-dimensional health state short form
SIGN The Scottish Intercollegiate Guidelines Network
SIQR The Revised Symptom Impact Questionnaire
SLE Systematic lupus erythematosus
SMR standardised mortality ratio
SNRIs serotonin noradrenaline reuptake inhibitors
SS symptom severity
SSRI Selective serotonin reuptake inhibitors
SW South-west quadrant
TCA Tricyclic antidepressants
UC Usual care
VAS Visual analogue scale
WPI Widespread pain index
WTP willingness to pay

Chapter 1: Thesis introduction

1.1 Introduction to thesis

Fibromyalgia (FM) is defined according to the American College of Rheumatology (ACR) as a chronic widespread pain and tenderness in at least 11 of 18 defined tender points (1). Patients with widespread pain who do not fulfil all the ACR criteria are given a diagnosis of chronic widespread pain (CWP) (1). FM is considered the third most common rheumatic disorder after low back pain and osteoarthritis, affecting 5% of all women in the USA and 2.8% of the UK general population (2, 3), while CWP affects 10% of the UK general population (4). ACR criteria and other evidence suggests that CWP and FM are overlapping disorders (5).

Evidence-based guidelines and other literature recommend a multi-professional or multidisciplinary approach to disease management in people with FM/CWP, combining both pharmacological and non-pharmacological treatments (6-10). The efficacy of implementing these programmes to people with FM/CWP has been investigated around the world. In the UK, use of pain management services (PMSs) is established but their clinical and cost effectiveness in routine clinical practice is less clear. The lack of evidence regarding the cost-effectiveness of the PMS prevents decision-makers charged with resource allocation from agreeing on the most effective management pathway to disease management in people with FM/CWP. Given that these services are resource intensive and may increase the cost to the NHS, evaluation is needed to demonstrate their cost-effectiveness.

To perform an economic evaluation, Quality-adjusted life-years (QALYs) measured by the EuroQoL- 3 Dimension (EQ-5D-3L) are the recommended outcome for cost-utility analysis. Data on QALY measures are not always collected as part of studies establishing the clinical effectiveness of health technologies. Lack of availability of such data can be a problem for researchers required to perform economic evaluations of those technologies. However, statistical technique known as “mapping” can be used to estimate health state utilities from different measures of health. In FM/CWP, no previous study performed mapping from FM/CWP specific measures such as the Revised Fibromyalgia Impact Questionnaire (FIQR) to the EQ-5D-3L.

1.2 Structure of the thesis

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

Chapter Two provides a review of the literature of the main subject areas that inform the research study namely FM and CWP, the nature of PMSs, their effectiveness and cost-effectiveness. Firstly, FM and CWP are defined and the key features with aetiology presented. The economic, personal, and social burden is then highlighted. The process of diagnosing FM/CWP and the accompanying challenges are discussed. The assessment of FM/CWP in clinical practice and clinical trials is also discussed. The management is presented before the challenges of managing those patients are considered. Then, a section regarding the current challenges presented in the published evidence, guidelines, and clinical practice for the diagnosis and management of FM/CWP. Secondly, the PMSs aims and relation to the biopsychosocial model are

clarified. The effectiveness and cost-effectiveness of PMSs in managing FM/CWP is then presented. Then an overview of PMSs in UK and Nottingham is discussed. A brief description on the recommended methods for the evaluation of PMSs is described. The section concludes with a summary of the literature review followed by a justification for the study and choice for methods used. Finally, the overall aim and objectives of the thesis are stated.

Chapter Three is a systematic review. Using standard SR methods, along with quality and reporting criteria, it identifies and critically appraises published economic evaluations of PMSs for the management of people with FM/CWP conducted from the time of the databases' inception to April 2016. The results are used to inform the design of the economic evaluation model in Chapter Five. The strength and methodological limitations of the retrieved studies are discussed.

Chapter Four is a prospective study which evaluates the feasibility of recruitment and determines the retention and follow-up rates of people with FM/CWP referred to two community based PMSs in Nottingham. It also explores patient characteristics, effectiveness, healthcare resource use (HRU), and treatment pathways of FM/CWP patients in PMS. This study highlights key methodological issues which inform the design of a future randomised controlled trial, such as sample size and the rate of recruitment and retention of patients. The main findings are presented and discussed after the methods. The chapter concludes by highlighting the strengths and limitations of the approach.

Chapter Five presents an indicative economic evaluation of PMS versus standard care in people with FM/CWP. The model is designed and reported according to quality and reporting criteria, and recommended approaches to ensuring model validity. Data from the feasibility study in Chapter Four is combined with published data from Chapter Three and other literature in a decision-analytic model. The aim of this evaluation is to assess the lifetime cost-effectiveness of PMSs compared with SC in the management of people with FM/CWP. It also aims to quantify the uncertainty around the incremental costs and benefits of PMSs compared with SC. The deterministic and probabilistic results are presented followed by one-way and scenario analysis. Finally, a discussion of the key findings, strengths, and limitations are highlighted at the end of the chapter.

Chapter Six is a mapping study in which data for 160 Spanish adults with FM is obtained from a researcher and used to estimate the EQ-5D-3L from the FIQR. The aims and objectives of this study are listed followed by a discussion of appropriate methodological approaches, including a summary of different econometric models and specifications used in mapping. The procedure for the choice of the best performance model is described. The mapping equation from the FIQR to the EQ-5D which was informed by the best performing model is presented. The chapter concludes with a discussion of the results followed by methodological strength and limitations.

Chapter Seven summarises the findings from Chapter 3 to 6 and concludes the thesis. This chapter begins by summarising the key findings and indicating where this thesis contributes to what we know about FM/CWP. The discussion then draws together the

findings from all four studies conducted, from which the implications for policy, practice, patients and research are set out. The chapter concludes by discussing key future work/recommendations that are needed as the next stages in this area.

Chapter 2: Literature review, aims and objectives

2.1 Introduction to the literature review

This chapter presents an overview of the literature related to the major topic areas covered in this thesis, which are FM and CWP, PMSs, and the effectiveness and cost-effectiveness of these services. The aim of the literature review is to:

- describe the incidence, prevalence, aetiology, and natural history of FM/CWP, and understand the level of disease burden at an individual and societal level
- review methods used to diagnose people with FM/CWP
- critique methods used to assess health status, or quality of life outcomes
- examine the evidence around the theoretical basis, design, effectiveness and cost-effectiveness of interventions to treat FM/CWP, including PMSs, in the management of people with FM/CWP.

The chapter finishes by summarising and synthesising the key gaps in knowledge in this area to provide a rationale for the research programme carried out in this PhD.

2.2 Fibromyalgia and chronic widespread pain

2.2.1 Definition, epidemiology, aetiology, and symptoms

Fibromyalgia is defined according to the ACR as a chronic widespread pain and tenderness in at least 11 of 18 defined tender points for at least three months (1). CWP is the core and a necessary criterion for the diagnosis of FM: patients presenting with widespread pain who do not fulfil all the ACR criteria (i.e. fewer than 11 tender points) are diagnosed with CWP (1). The ACR criteria and other evidence suggest that CWP and FM are overlapping disorders rather than being discrete diseases, in which the assessment and management would be similar (5, 11, 12).

FM is considered the third most common rheumatic disorder after osteoarthritis, affecting 5% of all women in the USA, and 2.8% of the general population of the UK and 4.7% in the other European countries (prevalence data for women, men, or specific age group in UK is not available) (2, 3), while CWP affects 10% of the UK general population (4). Women are more likely to be diagnosed with fibromyalgia than men, with a female-to-male ratio of six to one (13). The rate of FM in women increases with age, peaking (4.21%) between the ages of 55-64, and declining (1.75%) in older women aged 65 years and over, while the prevalence in men is stable across their lifetime (0.42%-0.58%) (13).

The incidence has been poorly investigated in FM/CWP, due to the difficulty in accurately identifying the onset of the disease (14). The first episode may have occurred many years previously, the timing of which is difficult to recall (14). Weir and colleagues interrogated a US-based health insurance claims database and found the age-adjusted incidence was 11.28 new cases per 1000 person-years for females and 6.88 cases per 1000-years for males (15).

FM/CWP is characterised by chronic (defined as more than three months in duration) pain that affects both sides of the body, above and below the waist (1). In addition, muscle tender points are often present at diagnosis. However, no consistent structural or functional abnormalities have been found. The specific aetiology of FM/CWP is not clearly understood (16). Dysfunction of central pain processing is considered to be a major contributing factor (17). Psychological, genetic, neurobiological and environmental factors are thought to be involved in its aetiology (18). People with FM/CWP report a wide array of somatic and psychological symptoms, including pain, fatigue, headache, unrefreshing sleep, depression and cognitive dysfunction (16).

These symptoms have a substantial effect on physical functioning and disability, resulting in limiting social participation (19, 20). Other conditions can coexist with FM/CWP such as osteoarthritis, inflammatory arthritis, and systemic lupus erythematosus (SLE), irritable bowel syndrome, anxiety, depression, and headache (12, 15).

2.2.2 Natural history of FM/CWP

When a person is diagnosed with FM/CWP, a complete remission, with complete resolution of symptoms, is rare, but the severity over time could change (21, 22). For example, more intense severity is prominent in periods of physical and/or mental stress and may decrease or be resolved during periods of better health.

The overall mortality among adults with FM/CWP is similar to that of the general population (23, 24). However, studies have found that depression (25, 26), chronic pain (27, 28), and sleep disturbance (29, 30) are risk factors for suicidal ideation and suicidal attempts. As these three different factors are cardinal symptoms in FM/CWP, an association between FM/CWP and suicide has been found (23, 31). Dreyer and others followed up 1217 confirmed cases of FM/CWP in Danish patients seen between 1984 and 1999 (23). The authors found that the standardised mortality ratio (SMR) of suicide was 6.5 (95 % CI; 1.8–16.7) in the FM/CWP population aged 19 to 70 years (23). Wolfe and colleagues examined the mortality rate in 8186 FM/CWP patients between the period from 1974 to 2009 in the US. The authors found that the SMR for suicide was 3.31(95% CI= 2.15-5.11) (24) when compared with the general population; however, they noted that the SMR was underestimated by the inaccurate

coding of some suicidal cases in the records to “accidental death” and it might be closer to 4 if 20% of accidents were misattributed.

All previous studies have demonstrated an increased risk of suicide in patients with FM (23, 24). Furthermore, a significant relationship between risk of suicide and the intensity of FM/CWP symptoms ($r=0.6768$, $p<0.0001$) was observed (32), indicating that higher FM severity patients are at higher risk of suicide.

2.2.3 The economic, personal and social burden

It has been found that FM/CWP has a massive impact on the quality of life. People with FM/CWP have a lower quality of life compared with the general population or individuals with other painful conditions that are considered as disabling, such as osteoarthritis, rheumatoid arthritis (RA), gout, SLE, herniated intervertebral disc and osteoporosis (33-37). Salaffi and others, for example, examined the health status burden of Italian people with FM (n=380) compared with the general population (n=1579) and RA patients (n=693) using the Medical Outcome Study Short-Form 36 (SF-36) (37). The authors found a statistically significant ($p< 0.0001$) impairment in individuals with FM/CWP in both the physical and mental component summary score (PCS and MCS) compared to the general population (FM/CWP vs general population: PCS mean (SD) = 38.5 (6.9) vs 49.6 (8.9); MCS mean (SD) = 32.8 (10.9) vs. 45.6 (8.4)). In comparison with RA patients (mean (SD); PCS= 33.5 (6.4), MCS= 40.2 (11.9), the FM/CWP patients showed a significant impairment in in the MCS ($p<0.001$) but better PCS ($p<0.01$).

The presence of FM/CWP can further deteriorate the health status in persons who previously had RA, SLE, or migraine (36). In a large US-based study of 2078 patients

with RA and FM/CWP (38), a significant impairment ($p<0.05$) in physical and mental components of the SF-36 was found when compared to a group of 9788 patients with RA alone. The mean (SD) of PCS and MCS in the RA and FM group were 23.5 (6.6) and 29.5 (12.8), whereas those of the RA patients without FM/CWP were 33 (10.2) and 46.4 (12.7). Previous findings highlight that FM/CWP contributes to the quality of life in affected persons (37, 38).

Regarding productivity and absenteeism, a substantial loss of function, work disability and work absenteeism were found to be associated with FM/CWP (20, 39-41). Patients with FM/CWP are often required to change their work as the severity of their symptoms increases (40, 42) and working hours are often reduced by up to 75% (40, 42). Moreover, studies reported that 46% to as high as 80.6% of people with FM/CWP have been reported as unemployed, as a consequence of disability associated with FM/CWP (43, 44). The risk of incidental loss of productivity is also reported in FM/CWP employees. A large US-based study of 8513 employees with FM/CWP, 8418 employees with osteoarthritis and 7260 employee controls, found that the rate of absenteeism in FM/CWP patients was almost three times that in the control group (29.8 versus 10.5 days per year, $p < 0.0001$) and significantly higher than employees with osteoarthritis (29.8 versus 25.7 days per year, $p <0.0001$) (41)

The economic burden of FM/CWP is substantial. People with FM/CWP are regarded as great utilisers of health care resources (45-47). A study performed between 1999 and 2007 assessed the total costs of hospitalisation charges per patient in the USA (48). The investigators found that FM/CWP patients' hospital costs reached approximately £766 million (US$1 billion) per patient over a 9-year period. Knight et al. found that the annual direct medical cost (2009 data) per patient was £5435, £1853,

and £368 in the USA, Germany, and France respectively (49), which was mainly attributed to prescription medications, and physician visits. The primary driver of differences in direct medical costs across the countries was medication costs, in which it cost 11 times higher in the USA (£2644) than in France (£241), and nearly six times higher than Germany (£468). Differences in medication costs in the USA were due to the higher utilisation rates of three approved medications for use in FM/CWP (pregabalin, duloxetine, and milnacipran), compared to none in Europe (49). It was also found that FM/CWP patients in France were less likely to consider their FM/CWP medication effective and less likely to be satisfied (49). Moreover, FM/CWP has significant indirect costs (costs attributable to reduced productivity and sick leave). The indirect costs per patient per year found in Knight et al.'s study represented the majority of all the costs, and ranged from about £5,000 to over £7,000 annually in the three countries (49).

In the United Kingdom, studies reported in the literature regarding the direct/indirect cost of FM/CWP patients are lacking. However, a study by Hughes et al., between 1998 and 2003, investigated the primary care resource use of FM/CWP of 2,260 newly diagnosed patients in the UK (47). The researchers found that these patients had more than twice as many prescriptions and medical visits per year when compared with the non-FM/CWP group (11 prescriptions and 25 visits per year in the FM/CWP group compared with 4.5 prescriptions and 12 visits per year in the controls). The direct cost of these patients' healthcare resource use (HRU) was not calculated in that study.

2.2.4 Diagnosis

The wide array of FM/CWP symptoms that may exist with the diversity of rheumatologic, medical, or psychological comorbid conditions present a diagnostic challenge for health care practitioners (HCPs). Currently, there is no laboratory diagnostic test for FM/CWP. The diagnosis is primarily a clinical diagnosis performed by HCPs. The criteria to diagnosis of FM/CWP has changed over time, **Table 1** summarise and compare four diagnostic criteria by the ACR.

Table 1. Summary of ACR diagnostic strategies

Diagnostic criteria	Pain	Regions of pain	Symptom
1990 ACR (1)	11 out of 18 tender-points[#]	3 out of 4 quadrants + axis	Not in the criteria
2010 ACR (50)	WPI* ≥ 7 in the last week	Any of 19 areas	SS* scale ≥ 5
2011 ACR (51)	WPI* ≥ 3 in the last week	Any of 19 areas	SS* scale ≥ 9
2016 ACR (52)	WPI* ≥ 7 in the last week OR WPI* of 4-6 in the last week	4 out of 5 regions (right\left upper region, right\ left lower region, axial region)	SS* scale ≥ 5 OR SS* scale ≥ 9

ACR the American College of Rheumatology; SS symptom severity, WPI widespread pain index
[#] Details of tender points in Appendix 2.
** Details of WPI and SS in Appendix 3.*

The first diagnostic criteria was The 1990 ACR criteria. It have been considered the gold standard to diagnose FM/CWP (53). The criteria require the presence of pain on both sides of the body and above and below the waist for at least three months. These involve the presence of at least 11 of 18 specific areas on the body regions (3 out of 4 quadrants and axis) that are sensitive to digital palpation (**Appendix 2**) (1). However,

this diagnostic technique does not take into account the symptoms commonly seen in FM/CWP and this procedure is hard to standardise, as many healthy people have tender points (54). The diagnosis of FM/CWP is undertaken mostly in the primary care setting. The tender point examination is rarely performed, and when it is performed, it mostly done incorrectly, because of the difficulty in performing it (55).

In 2010, The ACR produced new criteria that not only eliminated the tender points, but also changed the case definition of fibromyalgia to a disease defined by self-reported pain in 19 body regions (widespread pain index, WPI) and intensity of characteristic symptoms (symptom severity, SS), such as fatigue, sleep disturbance and cognitive symptoms (**Appendix 3**) (50). The WPI scale (score 0-19) quantifies the areas in which the patient had pain in the last week. The SS scale (score 0-12) scores the sum of severity of three symptoms (fatigue, waking unrefreshed, and cognitive symptoms) plus the extent of somatic symptoms in a scale from 0, no problems/symptoms to 3, severe problems/symptoms (see **Appendix 3** for further details). In the 2010 criteria a score of at least seven and five in the WPI and SS scale, respectively, is required for FM/CWP diagnosis. In 2011, modifications to the criteria were undertaken to develop a self-report version intended for use in clinical research (51). In addition, a modification in the scores was undertaken (WPI $\geq$ 3, and SS scale $\geq$ 9) to confirm the diagnosis of FM/CWP.

The two 2010 and 2011 versions identified more male patients, who met the 1990 criteria infrequently, because of an inadequate number of tender points (51, 56). HCPs prefer this approach as it does not require tender point examination and has the advantage of conceptualising the core symptoms of FM/CWP (57). The current and final version of these criteria was published in 2016 (52), which combined the previous

2010 and 2011 criteria into single set. The scores in the 2016 ACR criteria were either scores of WPI of at least seven with SS of at least five or scores of WPI of at least four with SS score of at least nine to confirm the diagnosis of FM/CWP (52).

A focus on FM/CWP diagnosis in practice

FM/CWP patients often lack a diagnosis for years due to the discrepancies in the recognition of symptoms, and in the validity of FM/CWP as a diagnosis (58). In 2013, Clark et al. performed a study in six European countries, including the United Kingdom, to identify the diagnostic practice in FM/CWP (59). In the European sample: 600 Patients (100 each from the UK, France, Germany, Italy, Spain and the Netherlands) and 1220 HCPs, including GPs and specialists, were surveyed. The results found that in European countries, patients see around 4 physicians and take around 31 months until they have a diagnosis of FM/CWP. When surveying the HCPs about the diagnostic procedure, 41% of GPs and 56% of specialists reported they were aware of the ACR criteria for diagnosis, but only 25% of GPs and 36% of specialists reported using the ACR in daily practice. An earlier survey by Perrot et al., in 2008, showed that 82% of GPs and 63% of UK specialists reported they received ‘very little’ or ‘no’ FM/CWP training (60). This percentage was the lowest when compared with other countries in the study (France, Germany, Italy, The Netherlands, Spain, Mexico and South Korea) (60).

2.2.5 Assessment of FM/CWP in clinical practice and clinical trials

Clinical outcomes

Fibromyalgia and chronic widespread pain, once diagnosed, are complex and subjective, which poses a number of assessment challenges. It is important that HCPs and researchers identify the core symptoms or domains of FM/CWP and check the psychometric properties of the outcomes measures i.e. utilise a valid (the degree to which a tool measures what it supposed to measure), reliable (the extent to which the instrument yields the same results on repeated measure) and responsive (sensitivity of the measure to detect the change) self-reported clinical outcome measures for these symptoms. Useful application of these outcome measures can determine if a meaningful change has occurred after the interventions.

A core set of six symptoms are recommended by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) as core domains to be assessed in all FM/CWP clinical trials: pain, tenderness, fatigue, patient global improvement, multidimensional function/health related quality of life, and sleep disturbance (61). Depression and cognitive dysfunction are considered as outer core domains. A wide variety of outcome measures have been used to capture the OMERACT domains for FM/CWP. **Table 2** illustrates outcome measures that can measure the domains recommended by OMERACT, with the respective psychometric properties.

Table 2. OMERACT's recommended domains in FM/CWP and outcome measures with respective psychometric properties

Fibromyalgia domain	Outcome measure	No. of items	Psychometric properties demonstrated for the outcome measure			Reference
			Validity	Reliability	Responsiveness	
Physical functioning/ Disability	Revised Fibromyalgia Impact Questionnaire (FIQR)- physical function	9	Yes	Yes	Yes	(62)
	Medical Outcomes Survey Short Form (SF-36)- physical function	36	Yes	Yes	Yes	(63)
Pain	Numeric pain rating scale (NRS)	1	NT	NT	Yes	(64)
	Visual analogue scale (VAS)	1	Q	Yes	NT	(65)
	Brief Pain Inventory (BPI)	15	Yes	Yes	Yes	(66)
	FIQR- pain	1	Yes	Yes	Yes	(62)
	McGill pain questionnaire (MPQ)	20	NT	NT	NT	(67)
Tenderness	FIQR- tenderness	1	Yes	Yes	Yes	(62)
Fatigue	FIQR- fatigue	1	Yes	Yes	Yes	(62)
	Multidimensional Fatigue Inventory (MFI-20)	20	Yes	Yes	Yes	(68)
Sleep	Medical Outcomes Study Sleep Scale (MOS)- sleep	12	Yes	Yes	Yes	(69)
	FIQR- sleep	1	Yes	Yes	Yes	(62)
Depression	FIQR- depression	1	Yes	Yes	Yes	(62)
	The Hospital Anxiety and Depression Scale (HADS)-depression	14	Yes	Yes	NT	(70)
Anxiety	FIQR- anxiety item	1	Yes	Yes	Yes	(62)
	HADS- anxiety	14	Yes	Yes	NT	(70)
Cognitive dysfunction	Multiple Abilities Self-report Questionnaire (MASQ)	38	Yes	Yes	NT	(71)
Health-related quality of life (HRQoL)	SF-36	36	Yes	Yes	Yes	(63)
	EuroQol (EQ-5D)	5	Yes	NT	Yes	(72)
Global improvement	FIQR global score	21	Yes	Yes	Yes	(62)

NT = not tested, Q=questionable.

The Revised Fibromyalgia Impact Questionnaire (FIQR) (62, 73) and the old version, the Fibromyalgia Impact Questionnaire (FIQ) (74), are extensively used as outcome measures in FM/CWP clinical trials as they can capture almost all the OMERACT domains for FM/CWP **(Table 2)** (62, 73). They have been cited in over 300 articles and translated into 14 languages (73). However, these two questionnaires are not generic health status measures that allow the calculation of quality-adjusted life-years (QALYs) and the subsequent performance of economic evaluation.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (75), the FDA Draft Guidance for Industry: Patient Reported Outcome Measures (76), and the OMERACT (61) organisations support the use of the Brief Pain Inventory (BPI) (66) to measure pain intensity in chronic pain patients. The BPI for pain intensity assesses the daily pain intensity through four items (pain intensity right now, pain intensity on average, worst pain, and least pain) on a 0 to10-point scale (0 = no pain, 10 = pain as bad as one can imagine). The BPI is sufficient to assess the intensity of pain and it does not require more than five minutes to complete by the patient. The mean of the four pain intensity items can be used as measures of pain intensity.

In summary, current evidence on the efficacy of FM/CWP interventions needs to be based on the assessment of core domains by using recommended outcome measures to ensure consistency between the studies and allow comparison between treatment alternatives. The health-related quality of life measures are discussed in the ‘Economic outcomes’ section below.

Economic outcomes

In the UK, QALYs are considered the most essential outcome measures to evaluate the cost-effectiveness of interventions. The National Institute for Health and Care Excellence (NICE) for England has recommended that all health technology appraisals (HTAs) should be presented by using an incremental cost per incremental QALY to allow for comparison with other HTAs (77). Many instruments can measure QALYs, such as EQ-5D (72), SF-6D (78), and HUI (79). However, the use of different instruments or measures results in generating different estimates of health state utilities. Consequently, many decision makers prefer a single instrument or approach for their HTAs. For example, NICE has endorsed the use of EQ-5D as the main instrument for their economic evaluation (77, 80). Two versions of the EQ-5D are available, the old three-level (EQ-5D-3L) and the new five-level (EQ-5D-5L), but the EQ-5D-3L is still currently preferred, for the time being, in economic evaluations (77, 80, 81).

Data on QALYs are not always collected as part of studies establishing clinical effectiveness of health technologies, but usually there are some sort of disease-specific health status measures used that are not designed to generate QALYs. Lack of availability of such data can be a problem for economic evaluations of those technologies. To bridge this gap, a statistical technique known as “mapping” or “cross-walking” can be used to estimate health state utilities from different measures of health. This technique uses regression models to inform the design of algorithms that can predict health state utility value using data from other measures of health. The mapping technique is well-established in other disease areas, such as in the case of rheumatoid arthritis, the mapping from the Health Assessment Questionnaire (HAQ) to EQ-5D-3L (82). In addition, the use of

mapping has become highly important for NICE: it has been found that over a quarter of NICE submissions to the HTA programme used a mapping technique in their submissions (83). Therefore, the NICE Decision Support Unit (DSU) has produced a technical support document that provides an overview of the key principles and methods of mapping to predict, or approximate, EQ-5D values (83). In addition, an online database of all published studies mapping to EQ-5D from other patient-reported outcome measures has been produced by the Health Economic Research Centre (HERC) (84).

There are two methods of mapping; statistical and judgment based mapping (83). Statistical mapping uses two datasets collected within the sample: data on the 'source' disease-specific measure (e.g. FIQR) and the 'target' preference-based measure (e.g. EQ-5D-3L). From these data, models or algorithms can be developed to predict the target preference-based measure, at the total score or index utility value, or the domain score, using the source outcome measure. These mathematical equations or models can be applied in data from other trials to predict utility values and to perform economic evaluations.

The other method of mapping is the judgemental based mapping, using the judgment of experts, which has been criticised in the literature for its irrationality or subjectivity (85). In addition, the validity of such an approach is questionable, and the only method to test the validity is by comparing the judgments against real data. Therefore, the statistically based mapping method is considered the better approach to predict utility values.

Mapping studies from FM/CWP specific measures to the recommended preference based measure, EQ-5D-3L are lacking. A systematic review published in 2010 described the

current practice in mapping studies to generic preference based measures in published and un-published literature (86). The review found 30 studies published between 1996 -2007. Upon examining the studies included in the systematic review, no mapping studies in FM/CWP were reported (86). Another search in the HERC database of mapping studies (last updated 16th May 2016) was performed; however, no mapping studies were found in FM/CWP (84). A further search was performed in other databases, and found a lack of mapping studies that map between FM/CWP specific measures, specifically, the widely used measure, the FIQR, to the NICE recommended measure for economic evaluations, the EQ-5D-3L.

Upon searching the literature, one published mapping study, which mapped the FIQR to the newer version of the EQ-5D, the EQ-5D-5L, was found (87). However, NICE stated in August 2017 that the 5L is not recommended for use until further quality research is conducted that explores the valuation set of the EQ-5D-5L (81). The lack of mapping research in any FM/CWP specific measure to EQ-5D-3L is problematic when economic evaluations of interventions in FM/CWP are needed.

2.2.6 Management

Treatment overview

Different strategies and treatments have been used to manage the symptoms of FM/CWP. These strategies include both non-pharmacological and pharmacological management (**Table 3**). The non-pharmacological management of FM/CWP is based on three categories: physical therapies, such as aerobic exercise and joint manipulation, acupuncture, and psychological therapies using cognitive behavioural therapy (CBT). The pharmacological management of painful symptoms of FM/CWP currently focuses around two classes of medicines: antidepressants, and anticonvulsants. **Table 3** shows the most used drugs for the treatment of FM/CWP.

Table 3. Non- pharmacological and pharmacological management of FM/CWP [a]

Non-pharmacological management	Pharmacological management [a]
Physical therapies Aerobic exercise Balneotherapy (heated pool treatment) Joint manipulation Electrotherapy **Psychological therapies** Cognitive behavioural therapy (CBT) Stress management programmes	**Antidepressants** ***Tricyclic antidepressants (TCAs)*** Amitriptyline Nortriptyline ***Selective serotonin reuptake inhibitors (SSRIs)*** Fluoxetine Citalopram Paroxetine ***Serotonin-norepinephrine reuptake inhibitors (SNRIs)*** Duloxetine [b] Venlafaxine Milnacipran [b] ***Norepinephrine reuptake inhibitors (NRIs)*** Esreboxetine **Anticonvulsants** ***Calcium Channel alpha-2-Delta Blockers*** Gabapentin Pregabalin [b]

[a] *not licensed for FM in the UK*

[b] *FDA approved for FM/CWP*

Regarding the efficacy of different management approaches in FM/CWP, a recent meta-analysis by Papadopoulo and colleagues examining the effectiveness of therapies across all domains included in the OMERACT list (pain, sleep, physical function, fatigue, anxiety, depression, and cognition) (7). The study included 46, 77, and 8 randomised controlled trials (RCTs) with pharmacological, non-pharmacological, and combination of non-pharmacological treatments, respectively. Standardised mean difference, 95% confidence interval, and the number of studies and participants for both treatments are summarised in **Table 4**. From the pharmacological interventions, based on moderate to high quality evidence, the analysis found that a statistically significant improvement was associated in most domains (all except sleep) with serotonin norepinephrine reuptake inhibitors (SNRIs), but with small effect on the pain and function domain (Cohen's d 0.20-0.49) and trivial effect (Cohen's d <0.20) on the remaining domains. A statistically significant improvement in four domains was associated with anticonvulsants (small effect: pain, sleep, fatigue; trivial effect: anxiety) and NRIs (moderate effect: function; small effect: pain, fatigue, and depression,). SSRIs were not significant in all domains.

Table 4. Estimates of standardised mean difference (SMD) with 95% confidence interval for pharmacological and non-pharmacological interventions in FM/CWP symptoms from Papadopoulo et al.'s meta-analysis (7)

Outcome	SMD (95 % CI)* [studies/participants]							
	SNRIs	**SSRIs**	**Anticonvulsant**	**NRIs**	**CBT**	**TCA**	**Exercise**	**Non-pharmacological combinations**
Pain	−0.22 (−0.27, −0.17) [12/6420]	NS	−0.28 (−0.37, −0.20) [5/2867]	−0.27 (−0.39, −0.15) [2/1374]	−0.24 (−0.45, −0.03) [9/437]	NS	-0.55 (-0.78,-0.31) [12/596]	−0.42 (−0.59, −0.24) [7/703]
Function	−0.16 (−0.22, −0.11) [8/5529]	NS	NS	−0.78 (−1.31, −0.25) [2/1267]	−0.38 (−0.70, −0.07) [3/166]	NS	-0.45 (-0.75,-0.15) [6/317]	−0.37 (−0.61, −0.13) [5/469]
Fatigue	−0.16 (−0.22, −0.11) [9/5633]	NS	−0.21 (−0.34, −0.08) [2/1235]	−0.43 (−0.68, −0.17) [2/1242]	NA	NS	-0.42 (-0.75, -0.10) [9/431]	−0.35 (−0.58, −0.12) [5/469]
Depression	−0.17 (−0.22, −0.11) [9/4803]	NS	NS	−0.35 (−0.60, −0.1) [1/252]	NS	-1.26 (-2, -0.5) [1/124]	-0.58 (-0.88, -0.29) [7/405]	−0.33 (−0.64, −0.02) [5/632]
Anxiety	NS	NS	−0.16 (−0.29, −0.03) [2/1245]	NS	−0.44 (−0.73, −0.15 [4/200]	NS	-0.50 (-0.88, -0.12) [4/266]	−0.33 (−0.59, −0.06) [5/470]
Cognition	−0.11 (−0.17, −0.04) [4/3984]	NA	NS	NS	NA	NS	NA	NA
Sleep	NS	NS	−0.44 (−0.52, −0.35)[5/2820]	NS	NS	NS	NS	−0.44 (−0.63, −0.26) [5/478]

CI confidence interval, NA not available, NS not significant, SMD standardised mean difference.
**Negative SMDs indicate a beneficial effect of the intervention. CIs not including zero are statistically significant and interpreted using Cohen's d definition (SMD= 0.2 -0.49, 0.5-0.79, and ≥ 0.8, as small, moderate, and large difference between groups, respectively.) if <0.2 difference between groups, the difference is trivial even if statistically significant.*

From the non-pharmacological interventions in Papadopoulo et al.'s meta-analysis (7), based on moderate methodological quality, a small meaningful improvement in pain, function, and anxiety was observed with CBT (7). Exercise provided less effective results, after excluding low methodological RCTs, with statistically significant improvement in pain (small effect), depression, and anxiety (moderate effect) (7).

In regard to the combined interventions, a small meaningful effect was observed in all FM/CWP symptoms except anxiety (data not available for cognition symptoms) when excluding low methodological studies in the sensitivity analysis (7). Non-pharmacological combinations in the studies were education and exercise (two studies), CBT and exercise (two studies), education, exercise, and massage (one study), education, exercise, and thalassotherapy (one study), psychotherapy, physiotherapy, sociotherapy, and creative arts (one study), and social support plus education (one study). Studies which evaluated combinations of pharmacological therapies or both the pharmacological and non-pharmacological therapies were excluded in Papadopoulo et al.'s meta-analysis (7). In summary, the study recommended a combined therapy of SNRIs and combined interventions, including exercise, appears to be the most promising mix of therapies for the management of FM/CWP (7).

Clinical practice guidelines in FM/CWP

Many evidence-based guidelines have been published by professional organisations addressing the management of FM/CWP: such guidelines have been issued by the American Pain Society (APS; 2005) (9), Canadian Pain Society (CPS; 2013) (10), Association of the Scientific Medical Societies in Germany (AWMF; 2012) (8), and the European League Against Rheumatism (EULAR; 2016) (6). However, inconsistency in their recommendations was observed. The APS, CPS, and AWMF assigned the highest ranking of recommendation to aerobic exercise, CBT, and amitriptyline (8-10). In contrast, the most recent EULAR guidelines assign the highest level of recommendation to exercise (6), contrary to the 2008 EULAR guidelines (88), which recommended pharmacotherapy.

As noted previously, the evidence-based practice guidelines are inconsistent in their recommendations, and this can be partially attributed to the composition of the guideline panels (AGREE checklist was not used to check the compliance of the guidelines). The panels of AWMF, APS and CPS were comprised of representatives of multiple disciplines engaged in the management of FM/CWP and also patients (8-10), whereas the EULAR panel consisted only of physicians, predominantly rheumatologists (6). As management of FM/CWP requires a range of specialists, the guideline panel should be also multi-professional to avoid any discipline-specific interpretations and recommendations. Furthermore, EULAR limited the evidence to RCTs (6). Systematic reviews and meta-analysis, which are considered the highest level of evidence, were excluded, in order to eliminate the effect of weak quality

studies. The three other guidelines used systematic reviews, meta-analysis, and clinical trials as sources of evidence (8-10).

All the guidelines emphasise the broad lack of evidence, which meant that some of the recommendations were purely based on expert consensus (6, 8-10). There was a lack of head-to-head clinical trials (most are placebo controlled trials, performed in durations not exceeding one year), which prevented the guideline panels from considering one single management approach as clearly superior to all alternatives. As a consequence, the management of FM/CWP will be based on trial and error, meaning that the patient may undergo a range of treatments that may vary between practitioners, before finding the most appropriate therapy.

Although there is a good deal of heterogeneity in the studies and recommendations included, all the guidelines agree that the main treatment should be multidisciplinary with a non-pharmacological focus (6, 8-10). In addition, these guidelines are all in agreement that therapy should be tailored to the individual needs of the patient.

In the UK, there are as yet no national guidelines addressing the management of FM/CWP or a licensed pharmacological treatment, whereas pregabalin, duloxetine, and milnacipran are approved for FM/CWP by the US Food and Drug Administration (FDA) (89).

A focus on the current FM/CWP management in practice

From the previously reported study by Clark and colleagues in European countries (n=600, 100 patients each from the UK, France, Germany, Italy, Spain and the

Netherlands), it was found that patients were taking a mean of four medications to treat their symptoms (59). Analgesics were the medications most prescribed by their HCPs (70 %), but 44% were taking additional over-the-counter analgesics. Non-pharmacological modalities were used, including relaxation techniques (48%) and exercise (45%). From the sample, only 20% (n=120) of patients who were using pharmacological and non-pharmacological therapy were satisfied (extremely/very) with their FM/CWP treatments. Country-specific data were not reported by the authors.

Following evidence regarding the levels of knowledge and awareness of UK GPs and specialists in FM/CWP (section 2.2.4) (60), the Fibromyalgia Association UK (FMA UK) published a report in 2014 calling for greater awareness and education of HCPs, and more research into FM/CWP suffering in the UK (90). The report emphasised the lack of investment in FM/CWP research, which was considered to limit the understanding of the conditions. The report also highlighted the need for an official review of FM/CWP treatments by NICE.

In conclusion, despite the improvements in the understanding of the condition, it appears that there is a delay in diagnosing FM/CWP for years and patients are under-treated globally. As a consequence, delay in diagnosis, and increase in health-care utilisation i.e. HCPs visits and self-managing behaviours, was observed in the previous study by Clarks and others (59).

Management challenges

To date, the lack of knowledge about FM/CWP aetiology has prevented the development of an effective treatment and all the available management strategies alleviate the severity of the symptoms without curing the condition. However, the management of FM/CWP is challenging due to many factors. Firstly, the pathophysiological mechanism is complex and not fully known (91, 92). This insufficient understanding has limited the research into mechanism-based therapies that could treat the patients.

In addition, the variety of FM/CWP treatments suggests there are difficulties in treating patients effectively, and evidence of their effectiveness is either uncertain or lacking (93). In addition, patients' pain and disability in chronic pain conditions is not only affected by the pathology, but by complex and dynamic interactions of physiological, psychological, and social factors that aggravate each other, causing chronic and complex pain (1, 94), for which the classical biomedical therapy has not proved sufficient (95). Given its multifaceted nature and the poor efficacy of current treatments, the integration of physical rehabilitation with psychological, behavioural and educational interventions in managing chronic pain has long been advocated (96-98). The concept of this type of rehabilitation is based on the biopsychosocial model and is the main aim of PMSs. Details of this model of care are described in the next section.

2.3 Pain management services in managing FM/CWP

2.3.1 Definition, membership, and location of PMSs

Patients with chronic pain such as FM/CWP present with multidimensional complications. Therefore, implementing a biopsychosocial approach which targets the multidimensional aspect of pain could improve management. This model of care can be delivered through a combination of interventions which integrates non-pharmacological therapies, including physical therapy (aerobic exercise and joint manipulation), and psychological (stress management programmes and cognitive behavioural therapy (CBT)), with pharmacological management (antidepressants, and anticonvulsants) (**Table 3**) (99).

The Pain Society of Great Britain and Ireland, now the British Pain Society (BPS), has clarified the aim of pain management services or programmes thus: '*To reduce the disability and distress caused by chronic pain by teaching sufferers physical, psychological and practical techniques to improve their quality of life*.'(100). This type of intervention should be patient-orientated to return the patient's sense of control over their condition, which is often lost in the medical consultation. Moreover, the relief of pain is not a declared aim of pain management services or programmes in the BPS. Although reduction of pain intensity is a desirable outcome, the focus is on the functional improvement.

In order to achieve the key aim of pain management, the BPS and the Faculty of Pain Medicine Core Standards for Pain Management Service in the UK (CSPMS) suggest that PMS requires input from medically qualified specialists (101, 102), including pain

consultants, rheumatologists, psychologists, physiotherapists, occupational therapists, nurses, and pharmacists. PMS can be located in primary care, specialist care hospitals (secondary care) or in specialised pain management units (tertiary care) (102). Treatment strategies provided by PMSs vary between different health care services in terms of the setting (i.e. inpatient or outpatient), specialities involved, and the intensity and nature of treatment modalities existing in the clinic (102). Different programmes have different treatment plans, as either individualised or standardised programmes, and each discipline has a specific method to design an individualised treatment plan tailored to the patient's needs (102). Regular communication with other PMS team and patient's GP is essential in such service (102).

2.3.2 Terminologies for the multi-professional team

Terms such as *multimodal*, *multicomponent*, *multidisciplinary*, and *interdisciplinary* are often used to describe these services in the literature (94, 103-105). The terms *multimodal* and *multicomponent* have not received a clear definition yet (104). Guesti et al. define *multimodal* interventions as the combination of multiple interventions, not necessarily provided by different professionals (104), whereas *multicomponent* denotes that the interventions are provided by different professionals, without clarifying how they are integrated (106).While, the other two terms clarify how these interventions are combined. *Multidisciplinary* means the involvement of multiple disciplines who stay within their boundaries (103). In multidisciplinary pain management, the disciplines are not necessarily located in the same facility (94), but they are considered multidisciplinary if they provide treatments with separate goals that do not take into account the contribution of other disciplines. The term *Interdisciplinary* refers to

various disciplines which are coordinated toward a common and coherent approach (103). Gatchel and colleagues stipulate that the interdisciplinary team should provide care under one roof at the same facility (94).

The International Association for the Study of Pain (IASP) (107) stratified pain centres according to the mix of professionals and interventions delivered: from a single modality clinic, such as a biofeedback clinic, to a *pain clinic* staffed by a single professional who can carry out more than one treatment, a *multidisciplinary pain clinic* with more than one professional group working under one roof and having frequent meetings and, ultimately, to a *multidisciplinary pain centre* which additionally carries out research (107).

From what was reported earlier, it can be seen that definitions of pain services vary throughout the literature. For example, the IASP provides a definition of *multidisciplinary* that is similar to the *interdisciplinary* definition in Choi et al. and Gatchel et al. (94, 103). Similarly, "pain clinic" as defined by the IASP is similar to the definition of "multimodal" by Giusti and colleagues (104). Due to the lack of consensus on the terminology, these terms have been used interchangeably in the literature (94, 103-105).

Historically in the UK, development of pain services was informed by the IASP guidance. However, with the NHS reconfiguration and the transfer of the management of long-term conditions back into community services, the Royal College of General Practitioners (RCGP) produced a guidance document (Pain Management Services: Planning for the Future) for Clinical Commissioning Groups (108) that moves away

from the IASP structure toward a pain management that is best delivered by a multi-professional team. The guidance document names the service as “pain management service” and the terms “multi-professional” and “multidisciplinary” are used as synonyms to describe the variety of professionals in the team rather than the integration between them.

Thus, in this thesis, following the RCGP guidance, pain management service (PMS) is used to define the clinics in the UK.

2.3.3 Effectiveness and cost effectiveness

As discussed previously, many international guidelines and other literature sources recommend a multidisciplinary approach, combining both pharmacological and non-pharmacological treatments, in managing patients with FM and CWP (6, 8-10, 88, 109), and the effectiveness of implementing these programmes has been investigated widely. A systematic review in 2008 reviewed the effectiveness of PMS in chronic pain conditions, including FM/CWP (110). Nine studies were included in the review (2 studies in Switzerland, 2 in Canada, 2 in Sweden, 1 in the Netherlands, and 1 in the USA). The results showed that the outcomes achieved by PMSs are better than those of standard medical treatment (110). However, the authors could not quantify the effectiveness of PMSs, or identify the most effective component, due to the great variability of the interventions, including their duration, setting and length of follow-up. In addition, the methodological quality of most of the studies that included RCTs was low; the method of randomisation was insufficiently reported, the evaluated outcomes were mainly pain, depression and coping, the inclusion criteria were limited

to females and sample sizes were small, which reduced the studies' ability to detect the exact benefits of PMSs (110). Although the aforementioned meta-analysis provided data about the effectiveness of PMS, evidence is sparse regarding their cost-effectiveness (111).

A comprehensive systematic review of the cost-effectiveness studies of PMSs in FM/CWP was undertaken in Chapter Three to identify and critically appraise published economic evaluations of PMSs for the management of people with FM/CWP. The strength and methodological limitations of the retrieved studies are discussed at the end of Chapter Three.

2.3.4 Pain management services in the UK

In the UK, the use of PMSs is well-established but their clinical and cost effectiveness in routine clinical practice is unclear. In 2008, the Chief Medical Officer for England and Wales (112) and the Scottish NHS (113) emphasised that the management of chronic pain should be a strategic priority. In 2011, a report from the first English 'pain summit' criticised the lack of clear guidelines and patchy services for management of chronic pain in England (114). The report states that access to effective pain management is a "fundamental right" that is often denied because the lack of clear standards. In addition, the report calls for a more multi-professional approach and nationally agreed commissioning guidelines to be developed, to reduce unwarranted variation between the services (114). According to these reports, the practice of managing pain through PMS is already established in the UK; however, there is a need

for research defining the role of PMSs and exploring their economic consequences and effectiveness in assisting patients with chronic pain in the UK.

2.3.5 Pain management services in Nottingham

In Nottingham, there are two PMSs located in the community served by the Nottingham West Clinical Commissioning group (CCG) and the Newark and Sherwood CCG. Nottingham West CCG is made up of 12 practices with approximately 93,600 patients. Newark and Sherwood CCG comprises 16 practices with 150,000 patients in a mixed urban setting with pockets of high deprivation.

Before establishing the PMSs, patients with FM and CWP were treated initially by their GPs. If treatment failed to improve the patients' outcomes, then referrals to physiotherapy, pain medicine or rheumatology may have been considered. However, the local commissioners in these CCGs considered that patients' pain, function and quality of life, as well as societal and health care costs, might be worsening due to the delay in diagnosis and treatment and the long waiting time to be referred to secondary care. As a result, the Nottingham West and Newark and Sherwood Community Pain Clinics were established in 2008 and 2013, respectively (115). At the time of the study, a consultant in pain medicine led the PMS, supported by a multi-professional team that operate out of four practices in Nottingham West CCG. Each PMS triages and manages patient referrals for all types of spinal and persistent pain. An individualised customised pain management plan is formulated and agreed with each patient. Patients may then have consultations with other members of the PMS team (including a physiotherapist, a biopsychosocial practitioner and a nurse) for supported self-care

management, or community services, such as physiotherapy, or more specialist secondary care services. Although the PMS provides many of the biopsychosocial elements, the approach is individualised for each patient.

2.4 Summary of the literature review

This literature review has highlighted the challenging nature of FM/CWP, caused by the unknown aetiology, as well as the complex and dynamic interactions between physical, psychological and social factors. Both conditions increase disability, sickness absence and the utilisation of health care resources representing major clinical, social and economic problems. No single treatment is adequate to control the wide range of symptoms and aspects of FM/CWP. It is therefore, sensible to develop a PMS that will consider all aspects of physical and psychological health and improve quality of life. The cost-effectiveness of applying PMS interventions on FM/CWP patients is unknown in the UK and the available published international studies lack quality. However, PMS is a widely used intervention to manage people with FM/CWP.

There was a lack of evidence for the use of mapping from the widely used measure in FM (Section 2.2.5), the FIQR, to the NICE recommended QALY measure for health technology assessment, the EQ-5D-3L. Using the recommended mapping technique to bridge this gap would aid in the future assessment of HTAs in FM/CWP interventions.

2.5 Study Justification

Anecdotally, local impressions are that patients are benefiting from this service and if it were expanded, patients in the Nottingham area (and the East Midlands more

generally) would benefit from better FM and CWP management. However, in Nottingham, as in other parts of England, financial constraints limit the possibility of expanding, or even the continuity of the current service. Therefore, it is important to evaluate the PMS to inform local decision-makers and commissioners about the effectiveness, and cost-effectiveness, in particular, of this service to allocate resources in an efficient manner.

Evidence and guidelines so far suggests that pain management clinics can be effective in both FM and CWP patients (6, 8-10, 88, 109), although the effectiveness of the PMSs developed in Nottingham is not known. Given that it is likely that these types of services are highly costly and require integration between health care sectors, the effectiveness, patient acceptability and cost effectiveness of community pain clinics needs to be investigated before this model of care is more widely implemented.

The National Health Service (NHS England) is responsible for delivering healthcare in England. The assessment of the cost-effectiveness of a service such as the PMS is an essential component in determining whether a service is approved for funding. Without evidence regarding the cost-effectiveness of PMSs, decision makers charged with resource allocation will not be able to agree on the most cost-effective management pathway in managing people with FM/CWP. As the PMS utilises a range of healthcare professionals working in a team, one implication may be increased cost to the NHS. However, better clinical outcomes may improve pain, functioning, and quality of life, which may reduce healthcare utilisation. Thus, a study is needed to assess the cost-effectiveness of the PMS.

Regarding the mapping from FM/CWP disease specific measures onto the EQ-5D-3L, lack of studies performed the statistical mapping is a challenge for researchers required to perform economic evaluations of technologies in FM/CWP. Although mapping studies considered a second choice from studies collect QALY measures to establish the clinical effectiveness, availability of such studies in FM/CWP is important.

2.6 Methodological Justification

The PMS intervention is considered a "complex" intervention, because of the number of interacting components within the clinic, the variety of intended outcomes, and the likelihood that the effectiveness is affected by the behaviours of those delivering or receiving the intervention (116). The service has a set of interacting interventions, involving different components of the health service, and the treatment pathway is reliant on the behaviour of both the health care professionals and patients. Moreover, pain has a multidimensional nature, thus requiring outcomes that measure all aspects of symptoms, such as pain severity, functional impact and quality of life. Therefore, the evaluation needs to be developed carefully.

There are known methodological challenges in evaluating complex interventions. The Medical Research Council (MRC) published a framework which recommends evaluating the intervention through observational and developmental work, followed by an exploratory trial before conducting the definitive evaluation. This process is required to identify key uncertainties in the design and assessment of the intervention and its evaluation (116). Therefore, before any comparative evaluative study of complex interventions is carried out, it is essential to characterise the intervention and

comparator, the target population and the treatment pathway. Moreover, this iterative approach of evaluation before conducting a definitive trial is required to answer essential methodological issues, specifically, the number and characteristics of people using the PMS, the outcomes best suited for an evaluation, and recruitment and retention rate of the sample. This prior work will contribute to the design of a robust evaluation. The MRC framework was designed to develop and evaluate complex interventions (116). However, the PMSs in Nottingham were already established and specific recommendations from the MRC regarding the evaluation were followed. Information regarding the development of the complex intervention is out of the scope of this thesis.

RCTs are designed to assess effectiveness, and involve randomisation and, usually, testing the treatment against a comparator, such as the standard care pathway, under strictly controlled trial conditions. There are key data that need to be identified and optimised before proceeding to RCT design. These data include the size of the recruited sample and the attrition rates in the study. The MRC guidance (116) suggests that before proceeding to a RCT, the researcher should be confident that all study procedures and the intervention to be tested have been fully optimised through feasibility work, because any alterations during the definitive study can cause delays, increase costs, and may confuse the results. For example, if n% drop out of the feasibility study, one can assume that a similar percentage may drop out in a definitive study, and thus the sample size for a definitive study may need to be adjusted to take this possibility into account, so that the study power remains unchanged if the same percentage of participants drop out. RCTs should be appropriately powered to detect

clinically meaningful effects, and will be larger in scale than a feasibility study, with the sample size and study duration often being informed from the previous feasibility work.

Conducting an economic evaluation alongside the RCT as a whole will provide more useful results for the decision-makers (116). However, due to the known difficulties and costs in evaluating such an intervention which require a prior feasibility work, the MRC recommends performing the economic evaluation through a modelling approach prior to the full scale evaluation (116). The modelling approach provides indicative cost-effectiveness results through the use of estimates from the feasibility work together with published estimates. This approach should be included in evaluations of complex interventions if at all possible, as this will make the results more useful for the decision makers (116). In addition, the results from the sensitivity analysis will provide information on how to improve the cost-effectiveness results in future. Moreover, in the case where the definitive trail was not funded, the results of the modelling technique can provide an insight of the likely cost-effectiveness of the complex intervention (116). Therefore, data obtained from the feasibility observational study in Chapter Four will be combined with published estimates of effectiveness and cost, in order to populate the indicative economic evaluation of PMS in managing people with FM/CWP compared with SC. The indicative economic evaluation will identify which parameters are most important for assessing cost effectiveness, and, therefore, which parameters need to be associated with minimal uncertainty. This will guide priorities for the study design and data collection in the next phase of the study.

When evaluating the cost-effectiveness of an intervention, data regarding QALYs are essential and should be included in the studies. However, in cases where such data are not available, statistical mapping from the disease specific measure to the recommended QALY measure, the EQ-5D-3L, can be used to obtain data on QALYs and perform the required economic evaluation. In FM, there is no published mapping study that maps from the FIQR to the EQ-5D-3L. The unavailability of mapping studies will limit the research regarding economic evaluation in FM/CWP managed by PMSs or any other services. Therefore, as part of the feasibility work in this PhD, statistical mapping from the FIQR to the EQ-5D-3L will be performed in Chapter Six in order to enhance future evaluations of cost-effectiveness.

2.7 Thesis aims and objectives

The overall aim of this PhD was to conduct a programme of feasibility work in preparation for the conduct of a definitive RCT of PMSs in managing people with fibromyalgia or chronic widespread pain, compared with SC. The programme included a systematic review, a feasibility observational study, an economic modelling, and a statistical mapping of FIQR to EQ-5D-3L.

The objectives for each chapter in this study were to:

Chapter 3: Systematic review

- Retrieve economic evaluation studies that evaluate the cost-effectiveness of PMSs for the management of people with FM/CWP.

- Summarise and critique the key elements of the retrieved economic evaluations, including study design, health status measures, healthcare resource use data, type of sensitivity analysis and the main economic evaluation results.
- Inform the design of the economic evaluation developed in Chapter Five using the results of the systematic review.

Chapter 4: Feasibility observational study

- Estimate the recruitment rate, retention rate, follow-up rates and assess the performance of study procedures.
- Explore the demographic characteristics of people with FM/CWP attending PMS.
- Explore the clinical outcomes of people with FM/CWP attending the PMS using patient reported outcome measures at baseline, three months and six months following the PMS's initial assessment.
- Explore details of HRU of people with FM/CWP managed by the PMS, using patient-reported health care resource use during the six months following referral.
- Explore treatment pathways of people with FM/CWP referred to PMSs.

Chapter 5: Indicative economic evaluation

- Develop an economic model that represents the treatment pathways associated with the management of FM\CWP through the PMS or SC.
- Populate the treatment pathway model with relevant probabilities, utilities, and cost.

- Identify and quantify the incremental costs of the PMS strategy compared with SC.
- Identify and quantify the incremental benefits of the PMS strategy compared with SC.
- Analyse the incremental costs per the incremental benefits of the PMS strategy compared with SC.
- Identify and quantify the uncertainty around the incremental costs and benefits of the PMS strategy compared with SC.

Chapter 6: Statistical mapping

- Map from FIQR as the source measure to the EQ-5D-3L utility score using direct mapping.
- Map from FIQR as the source measure to the EQ-5D-3L domains using response mapping.
- Identify the 'best' performing mapping function.
- Describe the relationship between fibromyalgia impact (FIQR) and generic health status using the result of the direct and response mapping.

Chapter 3: Systematic review of economic evaluation studies of pain management services for managing people with fibromyalgia or chronic widespread pain

3.1 Introduction

Many guidelines advocate the use of both pharmacological and non-pharmacological interventions using PMSs (88, 109), but the evidence for the cost-effectiveness of these services in FM and CWP is limited (111). Given that PMSs are resource intensive, evaluation of the available evidence is needed to demonstrate the cost effectiveness of these services in FM and CWP. This chapter presents the first systematic review of economic evaluation studies of pain management services to manage people with FM/CWP.

3.2 Objectives

The objectives of this chapter are to:

1- Retrieve economic evaluation studies that evaluate the cost-effectiveness of PMSs in patients with FM/CWP.
2- Summarise and critique the key elements of the retrieved economic evaluations, including study design, health status measures, healthcare resource use data, type of sensitivity analysis and the main economic evaluation results.
3- Inform the design of the economic evaluation developed in Chapter Five.

3.3 Methods

The review was conducted in accordance with Centre for Reviews and Dissemination guidance for undertaking reviews in health care(117).

Criteria for considering studies for this review

Types of studies

For this review, both economic evaluations conducted alongside RCT trials and model-based economic evaluations of PMSs for treating patients with FM/CWP were included.

Types of participants in studies

Criteria for inclusion in this systematic review were studies that had participants of either gender, aged 18 and over, with a diagnosis of FM/CWP according to the ACR classification criteria.

Type of intervention

As mentioned in the literature review (Chapter Two), there is no consensus around the exact terminology to refer to these services (94, 103-105). Therefore, an inclusive strategy of using all relevant terms (multidisciplinary, interdisciplinary, multimodal, multiprofessional, pain clinics and rehabilitation clinic) was adopted in order to identify all relevant publications, after which a detailed assessment for the components of the intervention was undertaken. This assessment was adopted in two Cochrane reviews performed on the same interventions and/or patients (118, 119), where PMS had to consist of at least two disciplines contributing to the management of an individual patient, such as a physician's consultation, plus a psychological, social or vocational intervention, or a combination of these. Thus, PMSs that offered fewer than two types of intervention within the service were excluded (118, 119).

Type of comparator

Studies comparing PMSs with any other treatment, including standard care (SC) or other PMSs in economic evaluations conducted alongside RCT trials and model-based economic evaluations were included in this review.

Location of intervention

Services administered in primary or secondary care settings were included, from any country.

Types of outcomes

Included studies had to have reported one or more patient outcome measures related to pain, functionality or quality of life.

Search strategy

An electronic search was conducted in both economic-specific databases and generic databases. The specialist economic evaluation databases included the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluation Database (HEED). Additional searches were carried out in Medline, Embase, PsycINFO, The Joanna Briggs Institute EBP Database, and Cochrane Central Register of Controlled Trials (CENTRAL), from the time of the respective database's inception to April 2016. The Cochrane library medical subject headings (MeSH), The Scottish Intercollegiate Guidelines Network (SIGN), and relevant systematic reviews in fibromyalgia and multidisciplinary interventions were used to identify relevant keywords and combined

with appropriate Boolean operators (118, 120, 121). The search was restricted to English language and full text sources.

Methodological quality assessment

Papers selected for review were assessed for methodological quality using the Cochrane Risk of Bias tool (**Appendix 4**) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) critical appraisal tool (**Appendix 5**) (122, 123).

The Cochrane Risk of Bias tool assesses the internal validity of the study and covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and performance bias (**Appendix 4**) (122). Within each domain, assessments are made for one or more items, which may cover different aspects of the domain, or different outcomes. A "low risk of bias" can be given to a study when at least 6 of the 12 criteria have been met. Studies which meet fewer than 6 of the criteria should be rated as having a "high risk of bias".

To assess the quality of reporting of the economic evaluation, the CHEERS checklist was used (**Appendix 5**). The CHEERS checklist has been supported by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) organisation (123); and endorsed by the BMJ and nine other publications (124). The checklist includes 10 areas, with 24 items: (1) title and abstract (2 items); (2) introduction (1-item); (3) methods (14 items); (4) results (4-items); (5) discussion (1-item); and (6) other, which is related to funding and conflict of interest (2-items) – **Appendix 5** describes the items included within the checklist, to evaluate the adequacy

of reporting information. The aim of the checklist is to improve the reporting of key criteria in economic evaluations; however, the quality of published studies can be evaluated indirectly, via assessment, using the checklist.

Data extraction

The researcher, Shiekha AlAujan, and a second reviewer, Saja AlMazrou, extracted data independently, according to a standardised form; this form included data on type of economic evaluation, patient characteristics (setting, inclusion/exclusion criteria), intervention characteristics (description of the PMS and comparator(s), duration of treatment and follow-up, components of the provided interventions and the speciality of medical staff involved in the provision of the service) and outcome measures. Any disagreements that arose between the reviewers were resolved through discussion or with a third reviewer.

3.4 Results

3.4.1 Study selection process

A primary search of databases retrieved 651 citations, which was reduced to 620 after the removal of duplicates. Based on reviewing titles and abstracts of the studies, 613 studies were excluded due to lack of relevance to the review question. Upon evaluation of the seven remaining studies, one included a simple intervention, administered by one healthcare professional, and was therefore excluded (125). Therefore, six economic evaluations were included in this review (126-130), in which one economic evaluation was published subsequent to another economic evaluation published by McBeth et al. (long follow-up study) (130, 131). The search strategy and details of the literature search and study selection are reported in **Figure 1** and **Appendix 6**.

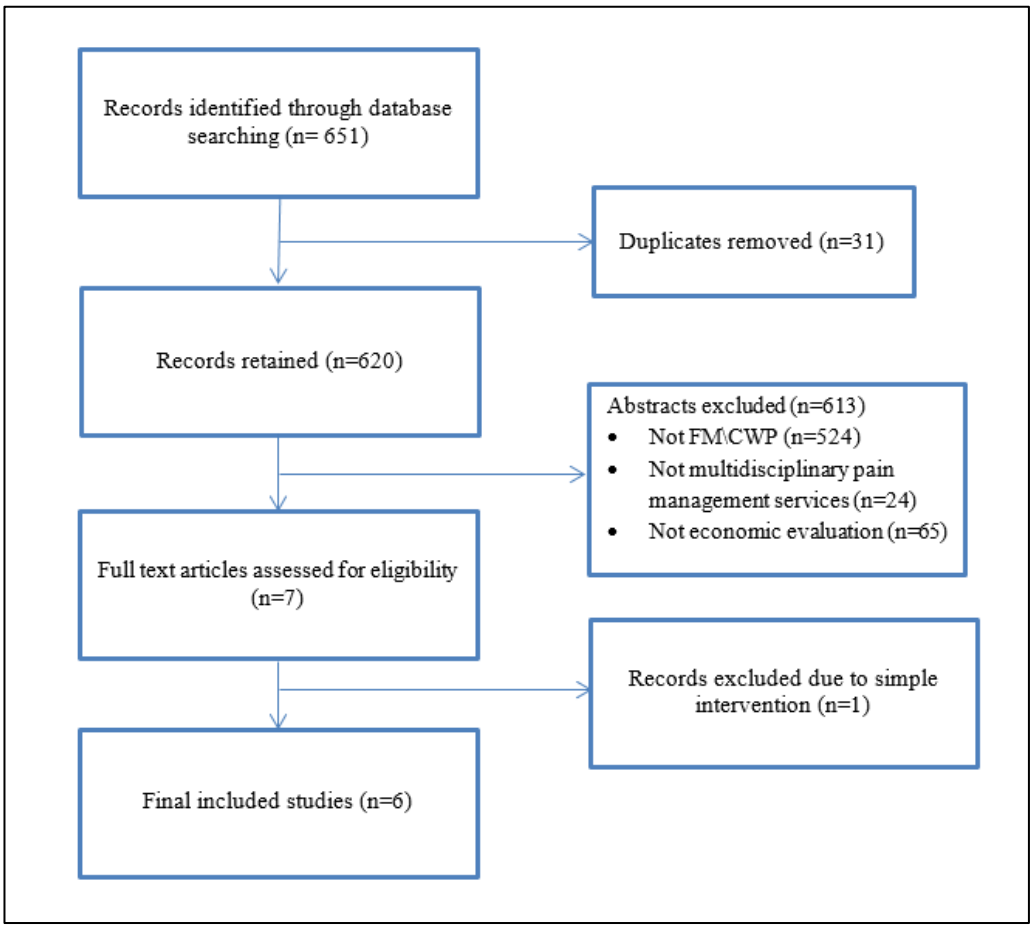


Figure 1. Flow diagram for included and excluded studies

3.4.2 Characteristics of included studies

Table 5 summarises the main characteristics of the studies. Two were from the UK (130, 131), two from the Netherlands (126, 129), and two from Spain (127, 128). Of the six studies, one was published in 1996 (129), two in 2007-2008 (126, 127), two in 2012-2013 (128, 130), and one in 2015 (131). The participants were aged from 18 to 75 years. One study evaluated a treatment programme devoted to females only (127). Two studies included participants with CWP diagnosis only (130, 131), and the remaining studies included only FM patients (126-129). The total sample size of the included studies varied from 33 to 442 participants. All the included studies reported cost utility

Table 5. Characteristics of included studies

Study ID, country	Setting, sample size	Participants' eligibility criteria	Comparative treatments*	Duration, follow-up period	Perspective	Type of cost, Cost year	Primary outcomes used
Goossens et al., 1996 (129) The Netherlands	Secondary care, 131	Patients aged 18 to 65, and met the ACR 1990	Cognitive intervention; Educational intervention	D: 6 weeks FU: 1 year	National health service	DMC, DNMC, IC 1993	Pain control, pain coping, tension and relaxation. Utility: Maastricht Utility Measurement Questionnaire (standard gamble and rating scale)
Zijlstra et al., 2007 (126) The Netherlands	Spa, 128	Patients aged 18-65 years, and met the ACR 1990	Spa treatment programme; SC	D: 2.5 weeks FU: 1year	Society	DMC, DNMC, IC 2000	Utility: SF-6D (calculated from SF-36) and VAS for general health
Gusi et al., 2008 (127) Spain	Swimming pool, 33	Women who met the ACR 1990.	Aquatic exercise; SC	D: 8 months FU: 8 months	National health service and society	DMC, DNMC 2005	Utility: EQ-5D-3L
Luciano et al., 2013 (128) Spain	Primary care, 216	Patients aged 18 - 75, who met the ACR 1990	Psychoeducational intervention; SC	D: 2 months FU: 1 year	National health service and society	DMC, IC 2009	Functional status: FIQ Utility: EQ-5D-3L
McBeth et al.,2012 (130) UK	Primary Care, 442	Patients aged 25 years or older with CWP, according to the ACR 1990	TCBT; Exercise; Combined therapy; SC	D: 6 months FU: 9 months	National health service	DMC 2009/2010	- Change in health using Clinical global impression change score - Utility: EQ-5D-3L
Beasley et al.,2015 (131) UK	Primary Care, 442	Patients aged 25 years or older with CWP, according to the ACR 1990	TCBT; Exercise; Combined therapy; SC	D: 6 months FU: 2 years	National health service	DMC 2009/2010	- Change in health using Clinical global impression change score - Utility: EQ-5D-3L

D duration of study, DNMC direct non-medical cost, DMC direct medical cost, FU follow-up period, IC indirect cost, NR not relevant, TCBT Telephone-delivered cognitive behavioural therapy, SC Standard care, VAS visual analogue scale.*Components for each intervention and disciplines involved are represented in Table 7.

analysis (n=6) (126-131), while Goossens et al. performed cost minimisation analysis, in addition (129).

Three studies were carried out in primary care (128, 130, 131), one was based at a secondary care clinic (129) and the other two studies provided the intervention in a setting other than healthcare clinics. In Zijlstra and colleagues study, Dutch participants in the intervention group travelled to a spa in Tunisia as part of the intervention, while the control group received SC in the Netherlands (126). Another study was set in a swimming pool, while the control group continued their SC with social support from the local FM/CWP association (127).

3.4.3 Study design

All economic evaluations were conducted concurrently with an RCT, in which all key parameters for the economic evaluation were provided using patient level data. Regarding the potential risk of bias, three studies had a low risk of bias (127, 130, 131) **(Figure 2)**. Lack of blinding of patients and the health care provider was an unavoidable risk in many (126-128, 130, 131) or all studies (the risk is unclear in Goossens et al.(129)), thus, performance bias was highly prevalent across the studies. All studies used an adequate method of randomisation except one (129). Only one study adequately reported the process of allocation concealment of participants (126), while in the remaining studies the process of concealment was either unclear or inadequately reported. Reporting participants' compliance to the intervention is essential to evaluate study outcomes and give a clear insight into the true effectiveness of the intervention. In this review, the compliance rate of patients was low in four studies (126, 127, 130, 131) and unknown in one study (128). Overall, the current

review found that 50% of included studies were associated with a high risk of bias **(Figure 2)**.

Most of the studies included met the majority of CHEERS quality criteria. However, none met all of the criteria **(Table 6)**. Details of these criteria are described below.

Figure 2. Summary of risk of bias (ROB) using the Cochrane Back Review Group Criteria (122)

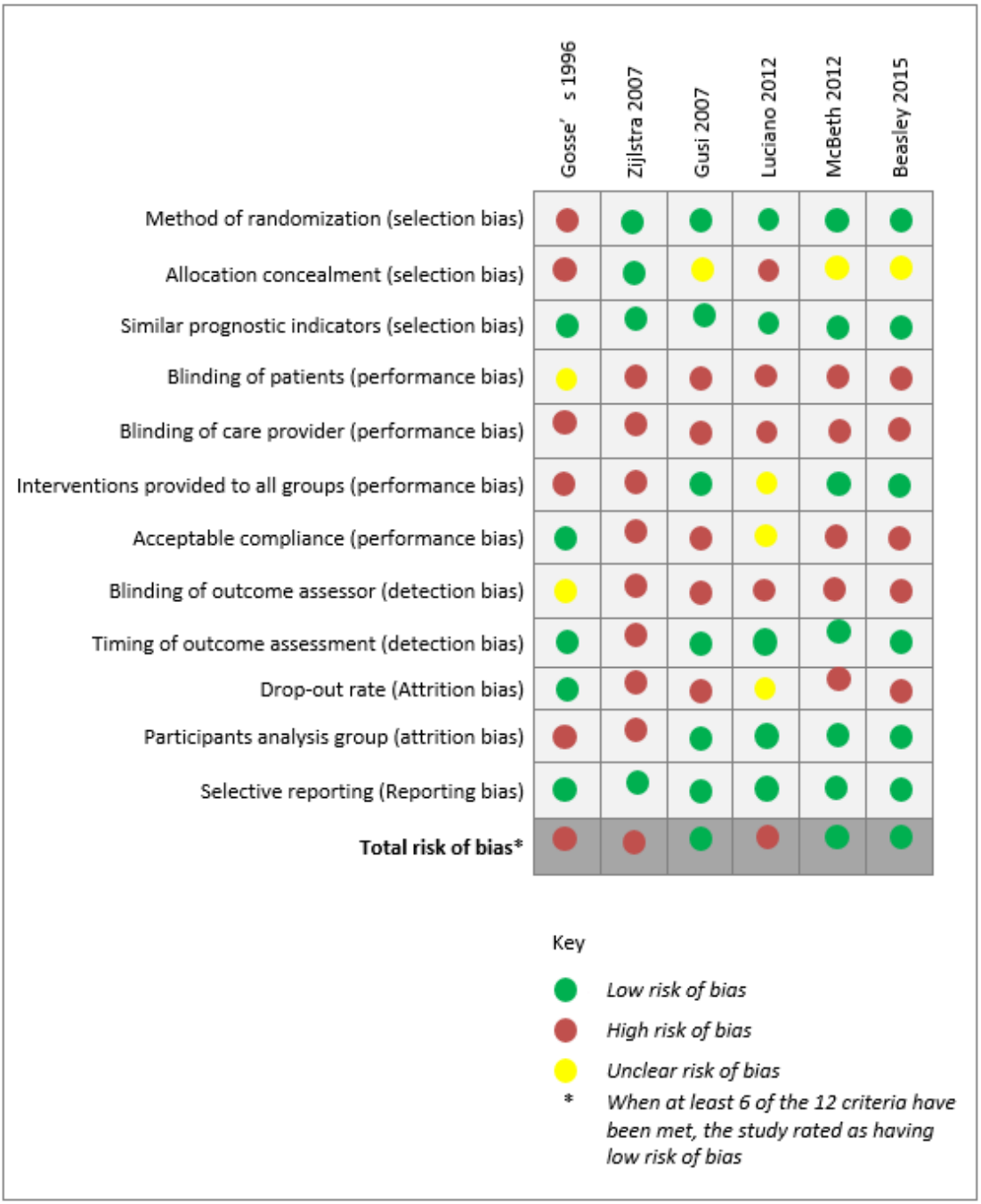


Table 6. Results of methodological quality assessment using CHEERS criteria (123)

Study ID	Target population and subgroup	Time horizon	Discount rate	Health outcomes	Measurement and valuation of preference outcomes	Cost and resource source	Currency, price year	Analytic method for skewness /missing data	Method to handle uncertainty	Report the results explicitly	Summarise findings, limitation	Source of funding
Goossens et al. (129)	Yes	Yes	N/A	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Zijlstra et al. (126)	Yes	Yes	Yes	Yes	No	Yes	Yes	For cost	Yes	Yes	Some	Yes
Gusi et al. (127)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Missing data only. No details about skewness	Yes	Not for cost	Yes	Yes
Luciano et al. (128)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Missing data only	Yes	No	Yes	Yes
McBeth et al. (130)	Yes	Yes	N/A	Yes	Yes but no further details	Reported but unclear	Yes	Significance of costing and uncertainty not tested	No	Insufficient information on cost	Some	Yes
Beasley et al. (131)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Insufficient information on cost	Yes	Yes

ICER Incremental cost-effectiveness ratio, N/A not applicable

Design and description of the pain management services

One key aspect of economic evaluation is the comprehensive description of the service, the comparators and their components (132). This allows assessment of the homogeneity of delivery, as well as allowing for assessment of reproducibility of the service to other settings. Four studies reported the details of the intervention in sufficient detail (127, 128, 130, 131). The PMS interventions varied between the studies in term of components, disciplines involved, and frequency of delivery, which made direct comparison of effectiveness or cost-effectiveness between the studies inappropriate (**Table 7**). The most commonly provided components delivered as part of the intervention were CBT (130, 131), education (129), exercise(127), or combinations of those treatments (126, 128-131). The treatment period and follow-up period varied considerably between the studies, ranging from less than three weeks (126) to eight months (127) of treatment and eight months (127) to two years (131)of follow-up. Details of the specific interventions and disciplines involved in the included studies are provided in **Table 7**. All studies provide the PMS in structured methods.

Many studies provided the intervention through group therapy (126-129), with a varied number of patients per group: e.g. Goossens et al. had a maximum of 6 patients per group while Gusi et al. had a maximum of 16 patients per group (127, 129). Other studies provided the intervention for each patient individually (130, 131).

Table 7. Components of each intervention in the included studies

Study ID	Comparative treatments	Components of the intervention: disciplines involved (frequency and length of each component)	Duration of intervention
Goossens et al., 1996 (129)	Cognitive intervention	Cognitive treatment: psychologist (12*90 min sessions). Education: one member of the interdisciplinary staff (12 sessions*2hrs sessions) (content is education, ended with physical exercise such as swimming or bicycling)	6 weeks of group therapy (maximum of 6 patients)
	Educational intervention	Education: one member of the interdisciplinary staff (12 sessions*2hrs sessions) (content is education, ended with physical exercise such as swimming or bicycling) Group discussion: led by the same psychologist of cognitive intervention group	
	Waiting group	-	-
Zijlstra et al., 2007 (126)	Spa treatment programme	Thalassotherapy (aquatic exercises in sea water and water pool): qualified hotel staff (7-8 sessions, 3hr). Exercise: (7sessions, 1hr, in groups of 4-5 pts). Education: rheumatologist, (7sessions, 1-1.5 hrs, groups up to 10). Recreational: available in the hotel + encourage patients to do exercise if no exercise sessions in the same day	2.5 weeks of group therapy
	SC	Usual treatment provided by physicians	-
Gusi et al., 2008 (127)	Aquatic exercise+ SC	Aquatic intervention included warming up, walking, aerobic exercise, etc. By qualified exercise leader (3 sessions\week for 1hr)	8 months of group therapy
	SC	Pharmacological treatment with social support by FM association	
Luciano et al., 2013 (128)	Psychoeducational + SC	Education: 4 general practitioners and 1 rheumatologist (5 sessions* 2 hrs) Autogenic training: a clinical psychologist (relaxation and exercise) (4 sessions*2 hrs).	2 months of group therapy (maximum of 18 patients)
	SC	Pharmacological treatment+ aerobic exercise counselling	-
McBeth et al.,2012 (130) and Beasley et al.,2015 (131)	Telephone-delivered CBT+ SC	By accredited CBT psychotherapist (initial assessment (45-60 min), then 7 weekly sessions (30-45min) delivered over 6 wks., 1 session at 3 months and 6 months post-randomisation).	6 months
	Exercise+ SC	By fitness instructor. Leisure facility and gym-based exercise programme consistent with the guidelines (induction session + monthly reassessment for 6 months-recommended dose 20-60 min), patient completed a diary to record attendance, duration, and type.	
	Combined intervention+ SC	Combination of Telephone-delivered CBT and exercise	
	SC	treatment by family physician	
CBT cognitive behavioural therapy, hrs hours, SC standard care			

The comparator

The comparator was well reported in most studies. The PMS was compared with SC (126-128, 130, 131), a waiting list (129), or another PMS intervention (129-131). Nevertheless, no comparator was similar to that in other studies, either in terms of components, or disciplines involved. Two studies (130, 131) defined SC as general pharmacological treatment alone. Other studies defined SC as pharmacological treatment combined with exercise consultations (128) or as pharmacological treatment combined with support from the FM association (127).

Outcomes

Many outcome measures were used in the studies (**Table 5**). Functional status was measured in one study, using the FIQ (74), along with the EQ-5D-3L (72) utility measure (128). McBeth et al. and the subsequent study by Beasley et al. used change in health measured by the Clinical Global Impression change score (133) with the EQ-5D-3L (130, 131). The remaining studies were based on either one utility measure e.g. EQ-5D-3L (127) or two utility measures e.g. SF-6D and the visual analogue scale (VAS) (126), or standard gamble with rating scale (129).

Appropriate adjustment of baseline characteristics, such as age and sex, using regression analysis is often necessary to more robustly estimate the independent effect of interventions on outcomes and costs. Five studies employed regression analysis (127-131). Missing data were handled analytically in four studies (127, 128, 130, 131), in which three reported the method used as multiple imputation (130, 131), and last

observation carried forward (LOCF) (128). Two studies failed to report statistical analysis of missing data, and results were presented for complete cases only, in which overestimation of the treatment effects may occur (126, 129).

Healthcare resource use and cost

The perspective of the economic evaluation influences the type of cost data selected for inclusion within the study. Adopting the societal perspective over other perspectives is considered ideal, due to the wider context of costs included, i.e. direct, indirect, and intangible costs. However, most economic evaluations are carried out from the perspective of healthcare providers, to allow for decision making under conditions of scarce resources. In this review, the perspective was reported clearly in all studies (**Table 5)**. However, valuation of cost elements in the studies was irrelevant to the viewpoint of the analysis in three studies (127-129). For example, Gusi et al. stated that their study took a societal perspective (127), but indirect costs were not collected in the study.

In economic evaluation, more precise cost estimates allow detection of the variation in cost between patients and interventions. Quantifying the cost for each patient, the micro-costing/ bottom-up approach (134), gives more accurate estimates than using the average cost method, or top-down approach. All the studies in this review used bottom-up costs. However, some studies did not report complete elements of costs, such as hospitalisation (127, 128), productivity and absenteeism (127), and non-prescribed medication cost (127, 128, 130, 131), or included costs irrelevant to the

perspective, e.g. productivity and absenteeism cost when the perspective is the healthcare provider (129).

Methods of estimating indirect cost, or productivity loss, can vary considerably. The human capital approach accounts for any hour not worked and calculates the productivity cost as the product of the total hours with the hourly gross earnings (including benefits) (135). Clearly, the human capital approach can overestimate the true cost of FM/CWP, by counting any hour where the individual is out of the work due to FM/CWP sickness or to receive health care for FM/CWP before the compensation of these hours by the absentee once he\she back to work or by colleagues (135). Instead, undertaking the friction cost method in analysing the productivity cost by counting the hours not worked until another employee takes over, will give more reliable estimate of productivity cost (135). Of the studies including productivity changes, one was based on the human capital approach (128), and one study was based on the friction cost (126). Goossens et al. used both methods (129), although the impact on results was not reported; however, it was mentioned that the cost estimate derived from the friction cost approach was much lower than from the human capital approach.

One of the key elements in economic evaluation is the discounting of cost and outcomes, which should be applied when the time horizon is longer than one year. This discount rate should be applied according to the national recommendations and quoted in the study, such as 3.5% in the UK. One study had a study period of over one year and applied the national discount rate for cost and outcomes (131).

The distribution of cost data is usually positively skewed and using parametric statistical tests to analyse the difference between groups is not generally appropriate if the sample is small. Non-parametric statistical tests or log transformation of data can be used, but have drawbacks, due to the failure to compare arithmetic means. Non-parametric bootstrapping is the preferred method, as it compares arithmetic means while avoiding distributional assumptions. Only one study used non-parametric bootstrapping (126). Log transformation was used in two studies to deal with skewness (130, 131). The remaining studies did not report their methods.

Dealing with uncertainty

Sensitivity analysis examines the robustness of the incremental cost-effectiveness ratio (ICER) through varying key parameters. Sensitivity analysis can be undertaken as one- and multi-way analysis, scenario analysis, threshold analysis, and probabilistic sensitivity analysis. One study did not perform sensitivity analysis (126), and four studies did not report the method used (128-131). Seven scenario sensitivity analysis were carried out in Gusi et al. (127). Uncertainty was examined in the included studies around cost only (129), or both cost and utility (128, 130, 131). One study assessed uncertainty around staff salary, rate of participation, distance to facility, and effectiveness (127).

Cost- effectiveness of pain management services

Incremental costs incurred and incremental QALYs gained for PMSs compared with SC are presented in **Table 8**. The cost-effectiveness of PMSs in the studies varied and were either inconsistent over different time periods or not robust to sensitivity analysis.

Luciano et al. reported that a PMS was dominant over SC at the follow-up after 1 year, without reporting the ICER (calculated ICER by the present author: €-215.49/0.12= €-1795.75/QALY for health care perspective and €-197.32/0.12= €-1644.33/QALY for societal perspective)(128). The sensitivity analysis proved the robustness of the ICER after imputing missing data. Gusi et al. found that, at 8 months PMS was more cost-effective per patient compared with SC, with an additional cost per QALY of €3947 from a health care perspective and €7878 from a societal perspective. All scenario sensitivity analysis supported the robustness of the ICER for both perspectives, except for the worst case scenario (ICER estimates of €75,455 and €159,545 per QALY for the health care and societal perspective, respectively).

Three studies showed temporary improvement in quality of life over different follow-up periods. McBeth et al. found that at 6 months, all active interventions were not cost-effective (130). At 9 months, PMS based on a telephone-delivered CBT was cost-effective with an ICER of £16542/QALY (UK threshold £20000-£30000 per QALY). However, this finding was sensitive to imputation of missing data (ICER= £39868/QALY). When a longer follow-up (2 years) was examined, TCBT was cost-effective compared with other interventions, with ICERs of £5917/QALY and

Table 8. Results of incremental cost, QALY and ICER presented in the included studies

Study ID	Comparative treatments	Incremental cost Mean (95% CI) [Mean (95%CI) in £]	Incremental QALYS Mean (95% CI)	ICER\ICUR Mean (95%CI) [£ Mean (95%CI) in £]
Goossens et al., 1996 (129)	Cognitive intervention vs. Educational intervention	0-1 Year US $1,623 * [£1180]	0-1 Year Rating scale: -0.027 **** Standard gamble: -0.022 ****	Not reported, as no statistical difference between the groups in QALYs
Zijlstra et al., 2007 (126)	Spa treatment programme vs. SC	0-6 months		
		€1,311 (-369 to 2,439) [£1161 (-326 to 2,160)]	SF-6D: 0.02 ** VAS for general health: 0.04 ***	€65,550/QALY (- 684,000 to 68,2000) [£58051/QALY (-605,756 to 603,985)] €32,775/QALY (- 375,000 to 273,000) [£29,025/QALY (-332,103 to 241,771)]
		0-1 year		
		€1,417 (-593 to 3156) [£1,255 (525 to 2,794)	SF-6D: 0.00 **** VAS for general health: 0.03****	Not reported, as no statistical difference between the groups in QALYs
Gusi et al., 2008 (127)	Aquatic exercise vs. SC	0-8 months Direct cost: €517 [£457] Total cost, including indirect cost: €1,032 [£913]	0-8 months EQ-5D-3L= 0.131 (0.011 to 0.29)	€3,947/QALY (1,782 to 47,000) [£3,495/QALY (1578 to 41623)] from health care perspective €7,878/QALY (3,559 to 93,818) [£6,976/QALY (3,151 to 83,086)] from societal perspective
Luciano et al., 2013 (128)	Psychoeducational intervention vs. SC	Complete cases, 0-1 year		
		Direct cost: €-215.49 (-615.13 to 287.81) [£190 (-544 to 254.8)] Total cost, including indirect cost: €-197.32 (-785.12 to 395.74) [£174 (-695 to 350)]	EQ-5D-3L= 0.12 (0.06 to 0.19)	PMS was dominant from health care and societal perspectives
		Imputed data, 0-1 year		
		Direct cost: €-225.28 (-548.69 to 200.89) [£199 (485 to 177)] Total cost, including indirect cost: €-188.99 (-629.76 to 317.09) [£167 (-577 to 280)]	EQ-5D-3L= 0.10 (0.04 to 0.15)	PMS was Dominant from health care and societal perspectives

* *P<0.001*; ** *P*<0.05; *** *P*<0.01 for difference between groups; **** No statistical difference between the groups in QALYs; [£] Converted to British Pounds at 2018 purchasing power parities. TCBT Telephone-delivered cognitive behaviour therapy, SC Standard care

Table 8 (continued)

Study ID	Comparative treatments	Incremental cost Mean (95% CI) [Mean (95%CI) in £]	Incremental QALYS Mean (95% CI)	ICER\ICUR Mean (95%CI) [Mean (95%CI) in £]
McBeth et al., 2012 (130)	TCBT; Exercise Combined therapy vs. SC	Complete cases, 0-6 months, compared with SC		
		TCBT: £385 (-0.26 to 793) Exercise: £540 (285 to 780) Combined: £777 (497 to 1,088)	TCBT: 0.005 (-0.014 to 0.023) Exercise: 0.004 (-0.009 to 0.020) Combined: 0.012 (-0.002 to 0.028)	TCBT: £76,695/QALY Exercise: £114,303 /QALY Combined: £63,858/QALY
		Complete cases, 0-9 months, compared with SC		
		TCBT: £ 345 (-177 to 887) Exercise: £567 (174 to 943) Combined: £842 (422 to 1,279)	TCBT: 0.021 (-0.011 to 0.060) Exercise: 0.008 (-0.022 to 0.042) Combined: 0.024 (-0.004 to 0.061)	TCBT: £16,542/QALY Exercise: £72,270/QALY Combined: £34,731/QALY
		Imputed data, 0-9 months, compared with SC		
		TCBT: £356 (-3 to 711) Exercise: £488 (209 to 789) Combined: £744 (428 to 1,069)	TCBT: 0.009 (-0.017 to 0.032) Exercise: 0.008 (-0.015 to 0.029) Combined: 0.016 (-0.005 to 0.037)	TCBT: £ 39,868/QALY Exercise: £ 61,165/QALY Combined: £49,220/QALY
Beasley et al., 2015 (131)	TCBT; Exercise; Combined therapy; vs. SC	Complete cases, 0-2 years, compared with SC		
		TCBT: £574 (-441 to 1,554) Exercise: £1,924 (782 to 3,295) Combined: £1,778 (690 to 3,009)	TCBT: 0.097 (-0.048 to 0.240) Exercise: 0.025 (-0.099 to 0.154) Combined: 0.047 (-0.086 to 0.182)	TCBT: £5,917/QALY Exercise: Dominated by SC Combined: Dominated by SC
		Imputed data, 0-2 years, compared with SC		
		TCBT: £554 (-121 to 1,297) Exercise: £1,256 (488 to 2,097) Combined: £1,453 (684 to 2,300)	TCBT: 0.140 (0.046 to 0.236) Exercise: 0.071 (-0.019 to 0.165) Combined: 0.096 (0.00 to 0.189)	TCBT: £3,957/QALY Exercise: Dominated by SC Combined: Dominated by SC

* *P<0.001*; ** *P*<0.05; *** *P*<0.01 for difference between groups; **** No statistical difference between the groups in QALYs; [£] Converted to British Pounds at 2018 purchasing power parities. TCBT Telephone-delivered cognitive behaviour therapy, SC Standard care

£3957/QALY in the complete case and when using multiply-imputed data, respectively (131). In Zijlstra et al., the PMS was cost effective over SC at the 6-month follow-up (ICER = £29,025/QALY using VAS of general health and £58051/QALY using SF-6D) (126). However, at the 1-year follow-up, the difference between costs and utilities was not statistically significant.

The evidence suggests that PMS are cost-effective treatments (**Table 8**); however, due to factors such as methodological weaknesses (method of utility valuation, comprehensiveness of costing method, and relevance of cost items to the view point of the analysis), and the heterogeneity and lack of standardised services in term of components, length of intervention, and length of follow-up. it was difficult to draw a definitive conclusion as to which are the most cost-effective pain management services in FM and CWP. Evidence on the lifetime clinical and economic benefits of these services was also lacking.

3.5 Discussion

This is the first review of economic evaluations of PMSs in FM/CWP and shows that there is limited evidence. Only six economic evaluations were found, and these reported that PMSs were generally more effective and more costly than the comparators. However, none met all the Cochrane risk of bias and the CHEERS quality criteria. Therefore, a conclusion about the cost-effectiveness of this type of intervention in general in this population cannot be drawn.

Well-designed and analysed economic evaluations are crucial to identify the real cost-effectiveness of PMSs. However, the variation in interventions, disciplines involved,

comparators, study setting, outcomes measures, type of cost, and length of follow-up, adds to the complexity of comparison, even with well-designed studies. Due to the complex nature of the intervention and challenges to design economic evaluations of these interventions, this review found that the cost-effectiveness of PMSs in the studies varied and was either inconsistent over different time periods or not robust to sensitivity analysis.

Most cost-effectiveness studies in this review adopted a time horizon of not more than one year (126-130). According to the Medical Research Council guidance on developing and evaluating complex interventions, long- term follow-up of complex interventions is crucial to reflect the persistence of short-term changes (132). However, no study in this review followed up the patients for more than two years to investigate longer term benefit. In addition, given the fact that both FM and CWP are chronic diseases affecting health and quality of life, a longer time horizon is preferred to estimate the costs, outcomes, and cost-effectiveness of PMSs on FM/CWP patients.

Generally, costing was the area of poorest quality in most studies, due to lack of completeness, relevance, quality, and analysis techniques which were not always optimal for economic evaluation. Whereas many studies reported costs related to the intervention, outpatient visits, and medication costs, few reported costs of hospitalisation, absenteeism (if relevant to the perspective), or non-prescribed medications. This is likely to have led to underestimation of costs and inaccuracies in determining incremental costs. Moreover, a non-parametric bootstrapping technique

was rarely used, even when this would have been the preferred method for analysing cost data.

There is no methodological consensus on estimating the productivity costs of chronic illnesses, resulting in methods varying greatly between studies, and thus wide ranges in estimates of costs. In this review, one study only attempted to address this lack of consensus by using both the human capital and friction cost approaches (129); however, the inadequate reporting of the study result hindered the comparison between the two methods in costing in this review. This methodological difference should be explored in future studies.

All the economic evaluations were conducted concurrently with a RCT, in which all key parameters for the economic evaluation were provided using patient-level data. This method is preferred, because it allows for stochastic results, i.e. mean and variance, and limits the uncertainty arising from obtaining the key parameters from a number of sources. However, due to the cost of performing RCTs, time periods are usually as short as possible. As both FM and CWP are chronic diseases affecting health and quality of life over an extended time period, longer follow-up studies are needed to estimate costs, outcomes, and cost-effectiveness and to determine the persistence of short-term changes. The MRC highlights the need for long-term follow-up of complex interventions and recommends the use of observational study design (116).

In this systematic review, one of the aims was to identify decision analysis models in order to inform the economic model discussed in Chapter Five. The key elements in an

economic model structure, including health states, transition probabilities, utilities, healthcare resource and cost were needed to inform the economic model. Decision analysis models have some advantages over economic evaluation alongside RCTs; firstly, the longer-term cost effectiveness of the intervention can be assessed. Secondly, they can provide decision makers with the best available evidence in a timely manner (136). However, no decision analysis models were identified in this review.

3.6 Conclusion

In summary, this systematic review found six studies which investigated the PMSs intervention in people with FM/CWP. The studies reported that PMSs were generally more effective but more costly than the comparators. However, due to methodological weakness and variability, this review is unable to make firm conclusions about the cost-effectiveness of this type of intervention in general in this population. The review highlights key design areas that researchers need to consider when conducting economic evaluations, including following standard design guidelines. However, effectiveness and cost-effectiveness over longer periods of time need further investigation, and it is likely that this will require use of routinely collected data and more extensive use of economic evaluation modelling approaches.

Chapter Five describes an indicative economic evaluation for PMS in people with FM/CWP. Data from this study and the next feasibility study in Chapter Four will be used in Chapter Five to extrapolate the lifetime clinical and economic benefit of PMS for patients with FM/CWP, using decision analysis modelling.

Chapter 4: Patient characteristics, treatment pathways, effectiveness, and healthcare resource use of PMSs in Nottingham for patients with FM/CWP: a feasibility study

4.1 Introduction

As established in Chapter Two, the PMS approach is advocated by clinical guidelines and can be effective for reducing severity of symptoms in people with FM/CWP. Given that these services are resource intensive, evaluation is needed to demonstrate their cost-effectiveness. Therefore, it is important to assess the clinical outcomes and perform a cost-effectiveness assessment in Nottingham PMSs' intervention and setting. Feasibility work to assess the methods and rates of recruitment is highly important prior to performing large-scale trials. Following specific MRC recommendations in evaluating complex interventions (116) , as the PMSs in Nottingham were already established, this chapter describes the recruitment feasibility and explores the effectiveness, HRU, and treatment pathways of a prospective observational study carried out at two community-based PMSs in Nottingham. This chapter reflects the methodology and necessary work required to evaluate an already established complex intervention for FM/CWP or any disease area. Information regarding development of such complex intervention in a health service is out of the scope of this thesis and the required information can be found in the MRC framework for the development and evaluation of complex interventions (116). Data collected in this study regarding the clinical and economic effects will be combined with data from a systematic review (Chapter Three) and other published data to model an indicative economic evaluation in Chapter Five.

4.2 Objectives

The objectives of this chapter are to:

1- Estimate the recruitment rate, retention rate, follow-up rates and assess the performance of study procedures.
2- Explore the demographic characteristics of people with FM/CWP attending PMS.
3- Explore the clinical outcomes of people with FM/CWP attending the PMS using patient reported outcome measures at baseline, three months and six months following the PMS's initial assessment.
4- Explore details of HRU of people with FM/CWP managed by the PMS, using patient-reported health care resource use during the six months following referral.
5- Explore treatment pathways of people with FM/CWP referred to PMSs.

4.3 Methods

4.3.1 Study design

In order to collect the main required data on patient characteristics, clinical outcomes, resource use and costs, a multicentre observational study design using a prospective patient level data was used. The protocol of this study was published in advance of the trial completion (AlAujan et al., 2016, see **Appendix 1**). In this study, it was difficult to identify people with FM/CWP from primary care clinics for the SC arm, therefore this study recruited participants from community-based PMS only.

4.3.2 Study setting

The study was carried out at two comparable community-based PMSs in Nottingham: Nottingham West CCG, and Newark and Sherwood CCG. The two services were operated by the same clinical staff, consisting of consultants in pain medicine, an

advanced physiotherapy practitioner, an advanced nurse practitioner, cognitive behavioural psychotherapist, and clinical nurse specialist.

The PMSs gave an initial agreement after being approached by one of the study team members (RK). A letter was sent to the PMS outlining information about the study. This was followed by a meeting with clinical staff to provide further information and to answer questions about the study.

4.3.3 Participants

Inclusion/exclusion criteria

Patients had to meet all of the following criteria:

- First time referred patients to PMSs with a diagnosis of FM or CWP according to 2011 ACR diagnostic criteria (51),
- Be aged 18 years or over,
- Have the ability to provide written consent for the study.

Patients with an unconfirmed diagnosis of FM or CWP, or who were aged less than 18 years old, or were unable or unwilling to provide written consent were excluded.

Recruitment

Initial approach to patients was made by the pain consultant. Patients were screened for suitability according to the inclusion/exclusion criteria and informed about all aspects pertaining to participation in the study. It was explained to potential participants that entry into the study was voluntary and that their treatment and care would not be

affected by their decision. It was also explained that they could withdraw at any time but attempts would be made to avoid this occurrence. In the event of their withdrawal it was explained that their data collected so far could not be erased and the researcher would seek consent to use the data in the final analysis where appropriate.

If the patient initially agreed to participate, an information pack was provided, which included a patient information sheet (**Appendix 7**), consent form (**Appendix 8**), patient demographic data collection form and functionality/pain intensity/health status questionnaires (**Appendix 9**), a HRU diary, and a self-addressed freepost envelope.

Patients were asked to provide contact details and preferred time for contact to arrange a telephone call with the researcher, to clarify the study and answer patient's questions, within three days. This period of time allowed the participant to review and understand the study pack material, sign the consent form and answer any questions regarding the patient's participation.

4.3.4 Intervention

Upon referral to PMS by their GPs, patients were triaged by the pain consultant and might have consultations with members of the PMS team (including a pain consultant, a physiotherapist, a biopsychosocial practitioner and a nurse) for supported self-care management, or community services such as physiotherapy, or more specialist secondary care services (115). The community-based PMS facilitates access to a wide range of diagnostic and treatment pathways, such as magnetic resonance imaging (MRI) investigations, rehabilitation programmes, medicines, and minor procedures such as trigger point injections. The management of the PMS is not a standardised programme,

where all patients with certain diagnosis have the same programme; instead, an individualised treatment plan is prescribed according to patients' needs. The description of the intervention did not follow the template for intervention description and replication (TIDieR) checklist (137), as it was difficult to describe the tailored intervention for each patient receiving PMSs during the six months study period.

4.3.5 Outcomes

Three types of outcomes are examined within this chapter; 1) outcomes attributed to the feasibility i.e. 'feasibility outcomes' and 2) demographic data and outcomes which would be of clinical interest i.e. 'clinical outcomes'; and 3) healthcare resource use and treatment pathways. A brief description of each type of outcome is presented below.

I. Feasibility outcomes

As suggested by the MRC (116), this study examined (1) recruitment, (2) retention of participants, and (3) the completion rate of questionnaires and health resource-use.

II. Demographic data and clinical outcomes

The demographic data and outcome measures assessed during baseline, three months and six months after referral are described below and summarised in **Table 9**.

Table 9. A summary of measures used and their main features

Name of measure	Sub-scales (No. of items)	Scoring method(s) used	Possible scores	Interpretation of scores	Recall period
FM and CWP functioning					
The Revised Symptoms Impact Questionnaire (SIQR) (62)	Physical functioning (9) Overall impact (2) Symptoms (10)	11- point Likert scale	0-100	higher scores = greater burden	Last 7 days
Pain intensity and interference					
Brief Pain Inventory (BPI) (66)	Pain severity (4) Pain interference (7) General questions (4)	11- point Likert scale	0-10	Pain severity = 0-10 Pain interference= 0-10 Higher scores= high impact	Today
Health status					
EuroQol-5-Dimension 3-level instrument (EQ-5D-3L) (72)	Descriptive items (5)	3 levels scoring	-0.594 - 1 (UK tariff)	Lower scores= lower quality of life	Today

Demographic data

The demographic and disease characteristics data collected included age, gender, marital status, living arrangement, work status, years since diagnosis with FM/CWP, prescribed and over-the-counter medicines for FM/CWP and comorbidities.

FM and CWP functioning- *The Revised Symptom Impact Questionnaire (SIQR):*

The non-FM variant of the FIQR (62), the Revised Symptom Impact Questionnaire (SIQR), was chosen over the FIQR, because the word fibromyalgia is omitted in the questions, so that patients who had been given a diagnosis of CWP by their GPs would be able to complete the questionnaire. SIQR is a 21-item, self-report measure using 0 to 10 scales with 10 being the most severe (62). SIQR measures three domains: physical functioning (nine items), overall impact (two items), and symptoms (ten items: depression, anxiety, memory problems, sleep, pain, stiffness, fatigue, tenderness, balance and environmental sensitivity), and a total summary score.

The scoring system is as follows: the physical functioning domain (0-90) is divided by three, the overall impact domain (0-20) is not transformed, and the severity of symptoms domain (0-100) is divided by 2. The SIQR total score (0 to 100) is obtained by adding the three domain scores, and higher scores indicate a greater symptom burden. The questions in the SIQR reflect the domains (pain, tenderness, fatigue, multidimensional function and sleep) recommended by the OMERACT as core dimensions to be assessed in all FM/CWP clinical trials (61). FIQR and SIQR were developed to overcome the problems associated with the original FIQ scoring, which

needs a ruler for the VAS measurements and the use of unwieldy mathematical equation to provide appropriate weighting to the domains and final scoring.

Pain intensity and interference *- The Brief Pain Inventory (BPI) - short form:*

This measure assesses the pain intensity (four items) and the impact (referred to as the interference domain, seven items) of pain on daily functioning with a recall period of the past 24 hours (66). The questionnaire also contains four general questions about pain and medicines. The PMS routinely use BPI in practice and collect scores at referral and at follow-up visits. Each item is scored on a 0-10-point scale (0 = no pain or interference, 10 = pain as bad as one can imagine or interferes completely). The mean of the four pain intensity or severity items can be used as measures of pain intensity/severity; the mean of the seven interference items can be used as a measure of pain interference. The BPI-short form is a modification of the Brief Pain Inventory - long form, which includes additional questions on demographics (date of birth, marital status, education, employment), pain history, aggravating and easing factors, treatment and medicine, pain quality, and response to treatment.

The psychometric adequacy of this questionnaire has been demonstrated in multiple types of chronic pain (138-140). As reported previously in the literature review, the use of BPI is supported by IMMPACT (75), the FDA Draft Guidance for Industry: Patient Reported Outcome Measures (76), and by OMERACT(61).

Health status *- Euroqol 5-dimension 3-level instrument (EQ-5D-3L):*

EQ-5D-3L is a standardised generic instrument that assesses HRQoL (72). It consists of five domains: mobility, personal care, daily activities, pain/discomfort and anxiety/depression. Three levels are defined for each domain, from which the patients have to choose the one that best reflects their situation. These 3 levels describe absence of problems in that dimension (level 1), moderate problems (level 2) and serious problems (level 3). A total of 243 (3^5) possible health states is produced and defined by a 5-digit code. These health states are translated into utility scores that are used to rate patients' HRQoL on a scale from 0 (as bad as death) to 1 (perfect health). Negative values are possible and indicate a health state that is worse than death. UK utilities range between -0.594 and 1.

III. Healthcare Resource use

Healthcare resource utilisation data was collected at the patient-level using prospective healthcare services use diaries, as these explicitly relate to the management of pain during their treatment at the pain service, including the following items: inpatient and outpatient visits to a specialist, or general practitioner, emergency department visits, nursing, social and psychiatric services, occupational and physical therapy, use of chiropractor services, prescription medicine costs and extra requirements, such as mobility equipment. Patient-level data or bottom-up resource use data was used over top-down(135), to obtain a more precise estimate of healthcare resource use for patients attending the PMS.

The patient diary was divided into six colour-coded parts, each part indicating a different type of medical service that the patient could obtain during each visit. The diary was designed as a tick-box and coloured to ease the filling in process for the patients. A section for notes was provided in the diary and in each section, if needed by the patient. The patients diaries used in this study had already been assessed for patient comprehension and acceptability have been approved for use in previous studies (141).

4.3.6 Patients and Public Involvement

The researcher liaised with Mr Antony Chuter in the design of all study pack content including the patient information sheet, the consent form, questionnaires and diaries. Mr Chuter is a patient and public involvement (PPI) representative who has extensive experience in patients' involvement in research in general. He has worked closely with the RCGP and the BPS, as well as working with the School of Pharmacy on previous community and primary care-based studies such as the New Medicine Service study. PPI opinion was sought during the designing of the study pack, including the patient information sheet, questionnaires, the HRU diary and the consent form. The PPI representative views informed the appropriateness of study pack content and the degree of burdensomeness to the patients.

4.3.7 Pre-pilot study

A pre-pilot study was conducted on three patients to examine the type, accuracy and practicality of the resource use data collection forms (11) and outcome measure tools. Demographic data, clinical outcomes of FIQR, BPI, and EQ-5D-3L, and HRU diaries were assessed in this study at baseline. All three patients did not show any difficulty in

filling the questionnaires and diaries. These patients were included in the final analysis, as no further amendments to the study design or data collection tools were made.

4.3.8 Sample size estimation

This was not an interventional study, so a sample size calculation was not required to derive an effect size. However, the sample obtained in this study will provide data to inform a future large-scale cost-effectiveness trial. The largest sample possible was also required to provide richer information about the patient cohort using PMS for FM/CWP. A target number of participants was estimated, based on the time and the documented number of patients referred in PMSs' annual referral report for the previous year (2013-2014). On this basis, 96 patients with FM/CWP were expected to be referred across the two PMSs over the one-year study period. However, data regarding the eligibility of patients from the previous year's records was not available. Therefore, the study aimed to recruit as many eligible participants as the study period allowed.

4.3.9 Baseline data collection procedure

At baseline, and after eligible patients were provided with the study pack, the researcher called the patients to answer any questions and to collect demographic data with baseline outcome measures by phone or, if the patient preferred, they could return it by post using the pre-paid envelope together with the consent form (**Table 10**).

Table 10. A summary of method and time of data collection

Name of data collected\outcome measure	Time point recorded	Method of recording
Demographic data	Baseline	Self-completed postal questionnaire or phone
The Revised Symptoms Impact Questionnaire (SIQR) (62)	Baseline 3 months 6 months	Self-completed postal questionnaire or phone
Brief Pain Inventory (BPI) (66)	Baseline 3 months 6 months	Self-completed postal questionnaire or phone
EuroQol-5-Dimension 3-level instrument (EQ-5D-3L) (72).	Baseline 3 months 6 months	Self-completed postal questionnaire or phone
HRU diaries	0-3 months and 4-6 months	Self-completed postal diary

4.3.10 Patient follow-up procedures

All outcome measures were posted to participants at three and six months from baseline, with pre-paid envelopes in order for the participants to complete and return them to the researcher (**Table 10**). Telephone calls and/or reminders to fill the diary were sent every three weeks. Non-responders were sent a second questionnaire within two weeks, and then contacted by telephone.

4.3.11 Data security and participant confidentiality

The data obtained from patients were 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 University of Nottingham and only the researcher had access to these data.

4.3.12 Data management

The participant data were received from the PMS as a spreadsheet, which contained pack number, participant name, NHS number, date of visit, contact number, preferred time slot and home address. This sheet was updated whenever new participant were added.

A new spreadsheet was created, which was also password protected, with the same participant details to enable the researcher to track the patients and keep a record of specific patient notes such the preferred method of filling the questionnaire, number of calls and reasons for declining if known. 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 participant reported their clinical and HRU data in paper format using questionnaires and diaries respectively. The data from the questionnaires were entered in STATA 14 (142).

4.3.13 Statistical analysis

All data were analysed using STATA 14 (142). Data were entered twice to establish quality of data entry. Recruitment rate, retention rate, study population and their outcomes on pain severity, FM/CWP physical function and impact, and quality of life were analysed using simple descriptive statistics. Descriptive statistics were also used

to compare study completers (patients who complete the three- and six-month follow-ups data) and non-completers (patients who failed to complete the three- and six-month follow-up data). Quantitative data from outcome measures was analysed descriptively, as the study was not powered to detect clinically significant effects. The analysis was treated as descriptive in nature and no attempts were made to assess the generalisability of the results (inferential analysis). Evidence recommended that null hypothesis significance testing is not appropriate for feasibility studies as the sample size is not powered (143).

Measures of central tendency and variance, including the mean, and median with interquartile ranges have been used to describe the full range of data at baseline and at follow-ups. It is recommended that it is more appropriate to report the median than the mean in data with a small sample size (144), because the mean is more sensitive to extreme values than the median. Even where outcome measures data are normally distributed, mean and SD can rarely be considered true interval data (144). However, reporting both values would allow comparison with other published studies, where possible.

Incomplete questionnaires were examined for patterns of missing data. As there is no universal method for handling missing data in a clinical trial, and the present study was not designed to detect an effect size, the last observation carried forward was used to estimate the missing data. This method is the most conservative analysis, as it assumes no change for people who drop out. For HRU data, missing data were not imputed,

because it is difficult to assume that the number of visits in the first three months will remain the same in the remaining study period.

4.3.14 Ethical approval

Ethics Research Committee and Research and Development approvals were granted before the study began. Ethical approval was obtained from NRES Committee North East – York on 23rd April 2015 (REC reference numbers 15/NE/0162) and from Research and Development Management department at Nottinghamshire Healthcare NHS Foundation Trust on 29th May 2015 (**Appendix 10 and 11**). Good clinical practice training for research training was undertaken by the researcher before REC and R&D approvals from the National Institute of Health Research NIHS was granted (**Appendix 12**).

4.5 Results

4.5.1 Recruitment challenges and ethical amendments

In the first four months of the recruitment, many challenges were faced by the researcher. The main challenge was the low recruitment rate. The study started on 7th June 2015, with the first patient presented to the PMS and being recruited on the 13th of July. The recruitment rate continued to be low during the summer period (June – October, nine patients presented and were recruited). Despite the estimated number of participants in the PMS annual reports being around 8 participants per month (96 participants per year), the actual recruitment from the PMS was very small. When the pain consultant was contacted to investigate the reasons for this, it was advised that the pain severity is lower in summer time than in winter time, therefore, patients do not attend appointments (Dr. Greg Hobbs, personal communication, July 2015). The number of newly referred patients to the PMSs was not a collected as data as part of this study.

Another challenge was one consent form was not returned immediately. This is may be due to the increased burden on participants to send both consent forms and questionnaires or that consent forms were accidently lost. Another reason was explored during a telephone call with one participant to fill in the questionnaire through the phone. The researcher identified that the participant was highly impaired by her FM/CWP, by her giving an answer as “pain as bad as you can imagine” for a BPI question “How much pain you have right now?”; also, the EQ-5D-3L utility index for the patient was -0.181 indicating a very low quality of life. Severe pain and low quality

of life might severely constrain the physical activity of the participant to be able to walk and place the mail in the post. Further communication, up to three times, with participants was undertaken to obtain the consent form either through the post or telephone calls based on participants' preference, otherwise the participant was considered to have withdrawn from the study.

In addition, three patients were invited in the period from June to October but declined to participate. The researcher investigated the reason for non-participation through telephone calls in order to explain the study and study the documents in case of confusion, especially the diaries, in which most of participants thought it needed a daily report. However, none of the participants who declined had problems in understanding the study pack, but stated other reasons for non-participation, such as having severe pain that impaired them from participation (n=2), and other commitments (n=1).

In order to improve the recruitment and increase the retention of participants in the study, a systematic review and a narrative review paper were consulted (145, 146), which recommend several methods to improve recruitment. Some of these methods had been already employed in this study, such as participants' preference for time of contact and method of returning the questionnaire to the researcher, telephone calls to follow up the written invitations, reminders and ongoing contact with participants, appropriate design and information of study pack, which was reviewed by a PPI representative, and regular contact with the recruitment staff. Another applicable method that was recommended and could be applied to this trial was the use of

financial incentives (145, 146). However, although the present study had no risk that would justify paying them for participation, the time needed for filling in the questionnaire and keeping a record for every visit to the NHS services for six months might be bothersome to some participants. Therefore, an inconvenience allowance was considered. The researcher had a discussion with a member from the research ethics committee at the University of Nottingham regarding the type and the amount of allowance which was considered ethically appropriate. From this discussion, we concluded that a £10 voucher per each filled questionnaire and HRU diary was reasonable. Therefore, each patient received a £30 voucher if the three questionnaires were completed.

Based on the literature recommendations and the initial recruitment process results, a substantial amendment was submitted to the NRES Committee North East-York on the 16th October and subsequently approved on the 4th November, 2015 (**Appendix 13 and 14**), to: 1) provide an inconvenience allowance of £10 vouchers for the participants for each filled questionnaire and healthcare resource use diary (total of £30), 2) obtain the consent form during PMS visit after the study had explained to participants and clinic staff would post it to the researcher thereafter, 3) extend the data collection period to September 2016 in order to compensate for the low recruitment during the beginning of the study.

The following part of the results describes the finding for the whole study sample.

4.5.2 Recruitment and retention rate

Over the whole study period, from June 2015 to September 2016, fourteen participants were eligible and invited to the study (data about the total number of FM/CWP patients who referred to the clinic during the study period was not collected as part of this study). Four participants declined to participate (reasons for non-participation: severe pain (n=2), other commitments (n=1), and unable to be reached (n=1). For the ten patients (71%) who consented to participate, retention was high (100% and 80% of recruited patients completed the three- and six-month study documents, respectively) **(Figure 3)**.

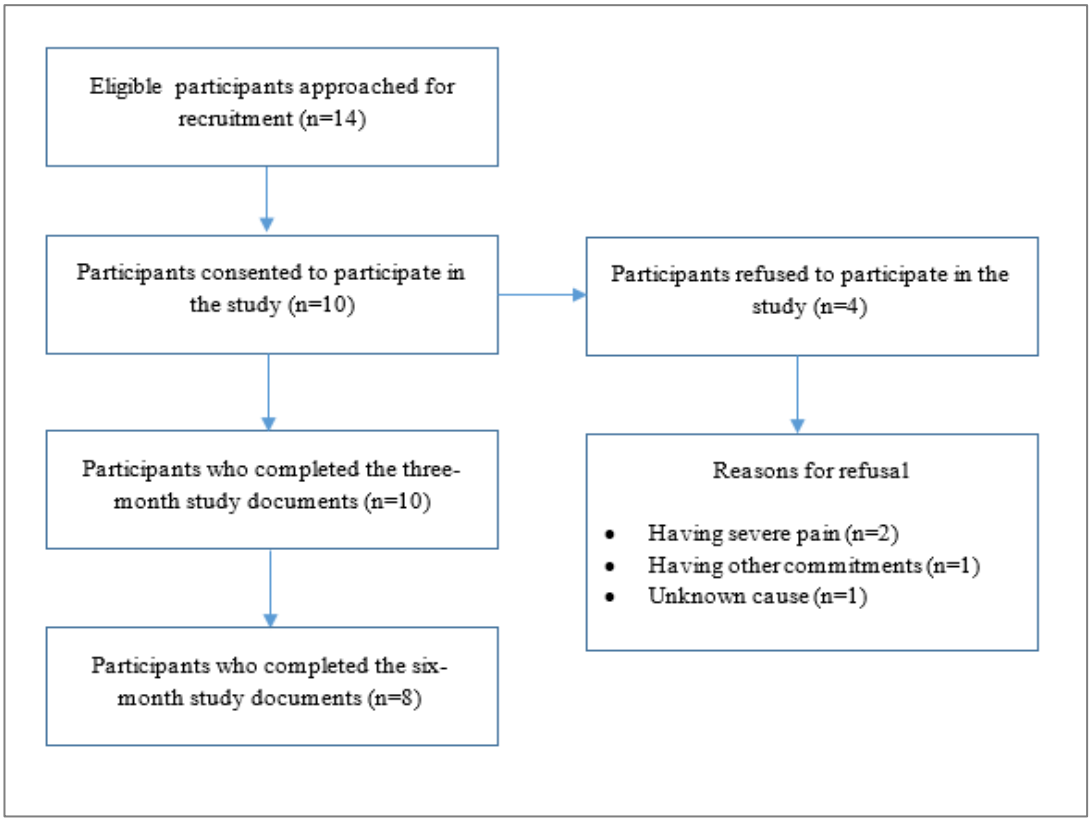


Figure 3. Flow diagram of recruited participant with FM/CWP during the study period

Investigation of baseline clinical outcomes revealed that a more severe outcomes was observed in participants who failed to complete the six-month data compared to participants who completed the study, in the means of pain severity, FM/CWP overall impact, and quality of life **(Table 11)**.

Table 11. Baseline characteristics of non-completers compared to completers

	Study completers N=8			**Study non-completers at six months N=2**		
	Mean	**Median**	**Range**	**Mean**	**Median**	**Range**
Age, years	41.1	42	21 - 55	41	41	37-45
BPI pain severity*	6.8	7.1	4.5 - 8.5	9.1	9.1	8.3-10
SIQR summary score#	70	70.8	56 - 88.3	81.2	81.2	73.2 - 89.2
EQ-5D-3L	0.1	0	-0.48 to 0.62	-0.1	-0.1	-0.18 to -0.07

**Higher means indicate greater level of pain. BPI severity levels: mild pain 1-4, moderate 5-6, severe 7-10. #Higher means indicate greater level of impairment. SIQR impairment levels: mild 0-38.99, moderate 39-58.99, severe 59-100.*

After the ethical amendments had been approved, one patient did not participate in the study, compared to three patients before the amendments. The reason for non-participation was unknown, due to inability to contact the patient by telephone. Overall, the recruitment and retention rates of participants were improved compared to the beginning of the study. Also, there were no missing data for all questionnaires at baseline and three- and six-month follow-ups for those who returned the questionnaires.

4.5.3 Baseline characteristics

Socio-demographic characteristics

Socio-demographic data are described in **Table 12**. The majority (n=8) of participants were female with a mean age (range) of 41 (21-55) years; five participants were married or cohabiting; half of the participants had a degree; all were of white ethnicity; four patients were full-time employees or students, while five of the sample were either employed part-time or unable to work. The majority (n=8) were unable to work for a period of time varying from 6 months (n=3), 1 year (n=3), and 2 years and more (n=2).

Table 12. Baseline socio-demographic and clinical characteristic of FM/CWP patients during study period

Socio-demographic variables	**N=10**
Mean age (range), years	41 (21-55)
Gender, female, n	8
Marital status, n	
Married/cohabiting	5
Single	3
Separated/divorced	2
Education level, n	
Secondary (GCSE, O level)	5
University (Degree)	5
Ethnicity, White, n	10
Work status, n	
Employed, full-time	3
Employed, part-time	2
Student, full-time	1
Unable to work	3
Housewife	1

History of FM/CWP and other medical problems

More than quarter of patients (30%) reported suffering from FM symptoms for one to three years while one patient had had FM symptoms for more than 10 years (**Figure 4**). The mean (range) number of prescribed and self-prescribed medicines for FM was 2 (0-4) and 1.25 (0-3), respectively (**Table 13**). The number of pre-existing co-morbidities ranged from zero to three among patients. Less than a quarter, two patients, had no other pre-existing co-morbidity while the remaining patients had at least one comorbidity. Among patients who reported pre-existing comorbidities, hypertension was the most reported comorbidity (n=3). Asthma (n=2), anxiety (n=2), and depression (n=2), and other medical conditions were reported such as migraine (n=1), systemic lupus (n=1), idiopathic generalized epilepsy (n=1), and prostate cancer (n=1). The mean number of medicines used for pre-existing co-morbidities was 3.4 (range from 1-14).

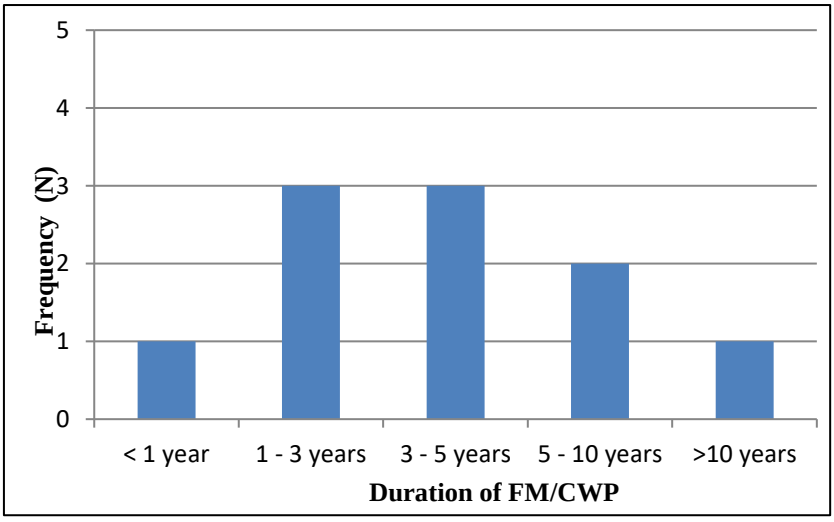


Figure 4. Stratification of patients based on FM/CWP duration in years

Table 13. FM/CWP medicines, comorbidities, and medicines for comorbidities for the ten patients

Item	Estimate
Mean number of current prescribed FM/CWP medicines (range)	2 (0-4)
Mean number of current self-prescribed medicines for FM/CWP (range)	1.25 (1-2)
Number of patients with comorbidities [a]	
Hypertension	3
Asthma	2
Depression	2
Anxiety	2
Other comorbidities	8
Number of comorbidities per patient	
None	2
One comorbidity	3
Two	3
Three	2
Mean number of medicines for comorbidities (range)	3.4 (1-14)

[a] *The number is more than ten because some patients had more than one comorbidity*

4.5.4 Clinical outcomes

As reported in section 3.3.10, the statistical significant changes in outcome measures over six months were not tested, because the feasibility study was not powered to detect an effect size. The effectiveness was reported to compare the results of outcome measures at baseline, and three and six months post-referral.

4.5.4.1 FM and CWP functioning (SIQR)

Details of FM\CWP patients' scores for each item, domain, and total SIQR are presented below.

I. Physical functioning

After three months following referral to PMS (**Table 14**), an improvement in all physical functioning items was observed except for 'brush or comb hair' and 'shopping for groceries', which did not change from baseline, while the items 'vacuum, scrub or sweep' and 'change bed sheets' had worsened. The median (IQR) overall function score decreased after three months from 20.5 (17-21.7) to 18.3 (15.8-21.5), indicating improved function.

At six months, an improvement was observed in four items ('brush or comb hair', 'vacuum, scrub or sweep floors', change bed sheet', and 'sit in a chair for 45 minutes') compared to the three-month score, and continued improvement was observed in one item ('walk continuously for 20 minutes') compared to baseline. The median of overall function (20, IQR; 16.8-20.7) improved when compared with baseline score (20.5,

IQR; 17-21.7) but not as the improvement in the three months post-referral to PMS (18.3, IQR 15-21.5).

Table 14. Comparison of physical functioning of SIQR at baseline, three months and six months post-referral

Function*	**Type of estimate**	**Baseline**	**3-months**	**6-months**
Brush or comb hair (0-10)	Mean (SD)	4.1 (2-6.3)	4.75 (2.5-7)	4.125 (1-6.2)
	Median (IQR)	5 (0-6)	5 (2.5-7)	3 (2.5-7)
Walk continuously for 20 minutes (0-10)	Mean (SD)	8.7 (7.5-9.8)	8 (6.8-9.3)	8.25 (7.4-9.1)
	Median (IQR)	9.5 (8-10)	8 (7-9.5)	8 (7.5-9)
Prepare a homemade meal (0-10)	Mean (SD)	5.5 (3.6-7.4)	5.6 (3-8.2)	5.9 (4-7.8)
	Median (IQR)	5.5 (4-8)	5 (3.5-9)	5.5 (4.5-7.5)
Vacuum, scrub or sweep floors (0-10)	Mean (SD)	8.8 (8.1-9.5)	8.9 (8.1-9.7)	8.25 (7.4-9.1)
	Median (IQR)	8.5 (8-10)	9 (8-10)	8 (8-9)
Lift and carry a bag full of groceries (0-10)	Mean (SD)	8.9 (7.9-9.9)	8.5 (7.5-9.5)	8.9 (8.2-9.6)
	Median (IQR)	9.5 (9-10)	8 (7.5-10)	9 (8.5-9.5)
Climb one flight of stairs (0-10)	Mean (SD)	8.2 (6.6-9.8)	5.9 (4.1-7.6)	7.8 (6.2-9.3)
	Median (IQR)	9 (7-10)	6 (5-8)	8 (7.5-9)
Change bed sheets (0-10)	Mean (SD)	7.6 (6.3-9)	7.8 (6.7-8.8)	7.5 (6-9.1)
	Median (IQR)	7.5 (7-9)	8 (7-8.5)	7.5 (7-9)
Sit in a chair for 45 minutes (0-10)	Mean (SD)	7.5 (6-9)	7 (5.1-9)	6.9 (4.8-9)
	Median (IQR)	9 (6-9)	8 (4.5-9)	7 (5-9.5)
Go shopping for groceries (0-10)	Mean (SD)	7.3 (5.5-9.1)	7.3 (5.1-9.3)	7.4 (5.1-9.6)
	Median (IQR)	8 (6-10)	8 (5.5-9.5)	9 (5.5-9.5)
Total function score (1-30)	Mean (SD)	19.2 (17.1-21.4)	18.4 (15.4-21)	18.7 (15.4-21.9)
	Median (IQR)	20.5 (17-21.7)	18.3 (15-21.5)	20 (16.8-20.7)

**Higher means indicate greater level of impairment.*

II. Overall impact

Table 15 shows the SIQR-overall impact domain for the patients across the study period. After three months post-referral to PMS, an improvement in all overall impact items was observed. In the overall FM/CWP impact score, the median (IQR) decreased after three months from 15 (9-20) to 14.5 (7-19). However, this effect was not sustained at six months post-referral (18, IQR; 15-20) and the impact score increased to greater than baseline.

Table 15. Comparison of overall impact domain at baseline, three months and six months post-referral

Overall impact*	**Type of estimate**	**Baseline**	**3-months**	**6-months**
My medical problem prevented me accomplishing goals for the week (0-10)	Mean (SD)	8.5 (7.5-9.5)	7 (4.7-9.3)	8.1 (6.1-10.1)
	Median (IQR)	8.5 (7-10)	7 (5-10)	9 (7.5-10)
I was completely overwhelmed by my medical problem (0-10)	Mean (SD)	6.1 (3.6- 8.6)	6 (3.2-8.8)	8 (5.8-10.2)
	Median (IQR)	6.5 (2-10)	7.5 (2-9)	9 (7.5-10)
Total Overall impact score (1-20)	Mean (SD)	14.6 (11.2-18)	13 (8.1-17.9)	16.1 (11.9-20)
	Median (IQR)	15 (9-20)	14.5 (7-19)	18 (15-20)

**Higher means indicate greater level of impact.*

III. Severity of symptoms

Table 16 represents the symptom severity scores during the study period. An improvement was observed in most symptoms (pain, stiffness, sleep quality, memory problems, tenderness to touch, and sensitivity to loud noises, bright lights, odours and cold) at three months post-referral to PMS. Depression remained unchanged from baseline and energy level together with balance problems were worse at three months. The total symptoms score at three months post-referral to PMS improved from baseline score (median (IQR): 36.5 (31.8-40.8) vs. 39.3 (33-44.5)). At six months following referral to PMS, level of energy, depression, and balance problems began to improve. Further improvement or sustained improvement were observed in the remaining symptoms, except tenderness to touch. The median of total symptoms' score at six months post-referral (32.3, IQR; 30.5-38.3) continued to improve from baseline (39.3, IQR 33-44.5) and three months post-referral (36.5, IQR; 31.8-40.8).

Table 16. Comparison of symptom severity domain of SIQR at baseline, three months and six months post-referral

Symptoms*	Type of estimate	Baseline	3-months	6-months
Pain (0-10)	Mean (SD)	7.8 (6.9-8.7)	6.9 (5.1-8.6)	6.8 (4.9-8.6)
	Median (IQR)	7.5 (7-9)	7 (6-8.5)	7 (5.5-8.5)
Energy level (0-10)	Mean (SD)	8.6 (7.7-9.5)	8.9 (8.3-9.5)	8.3 (7.7-8.8)
	Median (IQR)	8.5 (8-10)	9 (8-9.5)	8 (8-9)
Stiffness (0-10)	Mean (SD)	8 (6.7-9.3)	7.6 (6.5-8.8)	7.4 (6-8.8)
	Median (IQR)	9 (6-9)	8 (6.5-8.5)	7.5 (5.5-9)
Sleep quality (0-10)	Mean (SD)	9.3 (8.6-10)	8.3 (6.2-10.3)	8.5 (7.3-9.7)
	Median (IQR)	10 (9-10)	9.5 (7.5-10)	8.5 (8-10)
Depression (0-10)	Mean (SD)	6.7 (5.4-8)	6.8 (4.9-8.6)	6.4 (4.2-8.5)
	Median (IQR)	6.5 (5-8)	6.5 (5-9)	6 (5-9)
Memory problems (0-10)	Mean (SD)	7.3 (5.6-9)	6.9 (5.3-8.4)	6.4 (4.6-8.2)
	Median (IQR)	7.5 (6-10)	7 (6-8)	7 (6-7.5)
Anxiety (0-10)	Mean (SD)	7.8 (6-9.6)	7.1 (5.2-9.1)	6.1 (4.3-8)
	Median (IQR)	9 (5-10)	8 (5.5-9)	5.5 (5-8)
Tenderness to touch (0-10)	Mean (SD)	7.9 (6.4-9.4)	7.5 (6.2-8.8)	7.8 (6.3-9.2)
	Median (IQR)	8 (7-10)	7.5 (6-9)	8 (7-4)
Balance problems (0-10)	Mean (SD)	5.5 (3.1-8)	5.5 (3.5-7.5)	3.9 (1-6.7)
	Median (IQR)	6.5 (2-9)	7 (3-7.5)	4 (0-7)
Sensitivity to noises, lights, odours and cold (0-10)	Mean (SD)	7.9 (6.1-9.7)	7 (6.1-7.9)	5 (3- 7.1)
	Median (IQR)	9 (7-10)	7.5 (6-8)	4.5 (2.5-7.5)
Total symptoms score (0-50)	Mean (SD)	38.4 (34.3-42.5)	36.2 (32.4-40)	33.2 (29-37.3)
	Median (IQR)	39.3 (33-44.5)	36.5 (31.8-40.8)	32.3 (30.5-38.3)

**Higher means indicate a greater level of symptom's severity.*

IV. Total SIQR summary score

Table 17 represents the total SIQR summary score during the six-month period. Over the study period, a slight deterioration in the total SIQR at three months post-referral to PMS (median= 1.3 points from baseline) was observed, followed by an improvement at six months (median= 2.5 points from three months).

Table 17. Comparison of total SIQR summary score at baseline, three months and six months post-referral

Symptoms	Type of estimate	Baseline	3-months	6-months
SIQR Summary score (0-100)*	Mean (SD)	72.2 (56-89.2)	70.3 (46.7-89.2)	70.6(35.7-89.2)
	Median (IQR)	72.3 (60-80.3)	73.6 (56.7-80)	71.1 (38.2-82)

**Higher means indicate greater level of impairment. SIQR impairment levels; mild 0-24, moderate 43-59, severe 60-74, extreme impairment 75-100.*

4.5.4.2 Pain intensity and Interference (BPI)

Details of FM\CWP patients' scores for each item, and domain in BPI are presented below.

I. Pain intensity

At baseline, median pain intensity (IQR) was 7.8 (6-8.6) and after three months, the pain intensity improved to a median of 6.5 (5.8-7.4). The improvement in median pain intensity was not maintained at six months, but remained less than the baseline score (Error! Reference source not found.).

Table 18. Comparison of symptom severity domain of BPI at baseline, three months and six months post-referral

	Type of estimate	Baseline	3-months	6-months
Worst Pain (0-10)	Mean (SD)	8.3 (7.4-9.2)	7.1 (5.8-8.4)	7.1 (5.2-9)
	Median (IQR)	8.5 (7-9)	7.5 (7-8)	7.5 (6-9)
Least Pain (0-10)	Mean (SD)	6.4 (4.8-8)	5 (3.8-6.2)	4.9 (3-6.9)
	Median (IQR)	6 (5-8)	5 (4.5-6)	4 (3-6.5)
Average pain (0-10)	Mean (SD)	7.3 (6.1-8.5)	6.3 (4.7-7.8)	6.8 (5.3-8.2)
	Median (IQR)	8 (6-8)	7 (5-8)	7.5 (6.5-8)
Pain right now (0-10)	Mean (SD)	7.2 (6.2-8.2)	6.4 (4.9-7.8)	6.8 (5.1-8.9)
	Median (IQR)	7 (6-8)	7 (6-7.5)	7 (6-8.5)
Mean pain severity (0-10)	Mean (SD)	7.3 (6.3-8.3)	6.2 (4.9-7.5)	6.3 (4.3-8.4)
	Median (IQR)	7.8 (6-8.6)	6.5 (5.8-7.4)	6.6 (5.6-7.6)

**Higher means indicate a greater level of pain severity.*

II. Pain interference

In the pain interference domain of the BPI, patients were asked to rate seven interference items; general activity level, mood, walking ability, normal work, relation with other people, sleep, and enjoyment of life. The overall symptoms score (0-10) was then calculated.

Table 19 reports the interference scores during the study period. An improvement was observed in all interference items at three months post-referral to PMS, except the normal work item. In summary, the median pain interference score at three months (median, IQR; 7.8, 6.6-9) was improved from the baseline score (median, IQR; 8.6, 7.6-9.5).

At six months post-referral to PMS, further or sustained improvement were observed in mood, relations with other people, and sleep. The remaining items started to deteriorate but still not below baseline levels. The median pain interference score (7.9, IQR; 6.1-9.2) was improved from the baseline (8.6, IQR; 7.6-9.5), but was not superior to that at three months post-referral (7.8, IQR; 6.6-9).

Table 19. Comparison of pain interference domain of BPI at baseline, three months and six months post-referral

Interference item*	Type of estimate	Baseline	3-months	6-months
General activity level (1-10)	Mean (SD)	8.3 (7.2-9.1)	7.8 (6.2-9.3)	7.3 (5.5-9)
	Median (IQR)	8 (7-10)	7.5 (6.5-10)	8 (5.5-9)
Mood (1-10)	Mean (SD)	8 (6.6-9.4)	7.3 (5.4-9.1)	7.12 (5.2-9)
	Median (IQR)	8.5 (5-10)	7.5 (6.5-9)	7.5 (6-9)
Walking ability (1-10)	Mean (SD)	7.9 (6.2-9.6)	6.6 (4.9-8.4)	7.3 (5.2-9.3)
	Median (IQR)	9 (5-10)	7 (4.5-9)	8.5 (5.5-9)
Normal work (1-10)	Mean (SD)	7.7 (6.4-9)	7.9 (6.6-9.1)	7.6 (6.1-9.1)
	Median (IQR)	7.5 (6-10)	8 (6-9.5)	8 (7.5-8.5)
Relation with other people (1-10)	Mean (SD)	7.2 (5.8-8.6)	7.4 (5.68-9.1)	6.5 (4.6-8.4)
	Median (IQR)	8 (5-8)	6.5 (6-10)	6.5 (5-8.5)
Sleep (1-10)	Mean (SD)	7.7 (6.2-9.2)	7.1 (4.8-9.4)	7 (4.8-9.2)
	Median (IQR)	8.5 (6-10)	8 (4.5-10)	7 (5-10)
Enjoyment of life (1-10)	Mean (SD)	8.7 (7.5-9.9)	8 (6.3-9.7)	8.1 (6.3-9.7)
	Median (IQR)	10 (6-10)	8.5 (6-10)	9 (7-10)
Pain interference (1-10)	Mean (SD)	7.9 (6.8-9.1)	7.4 (6.1-8.8)	7.3 (5.7-8.8)
	Median (IQR)	8.6 (7.6-9.5)	7.8 (6.6-9)	7.9 (6.1-9.2)

** Higher estimates indicate greater levels of pain interference*

4.5.4.3 Quality of life (EQ-5D-3L)

The result for EQ-5D-3L quality of life for patients are shown in **Table 20**. The table shows that utilities have improved at three months (median, IQR; 0.25, -0.52-0.57) from baseline (-0.02, IQR; -0.43-0.6); however, the effect was not sustained at six months post-referral to PMS (-0.05, IQR; -0.19-0.54).

Table 20. Comparison of quality of life at baseline, three months and six months post-referral

	Type of estimate	**Baseline**	**3-months**	**6-months**
EQ-5D-3L (-0.594**-1)***	Mean (SD)	0.03 (-0.48-0.62)	0.19 (-0.59-0.69)	0.04 (-0.24-0.69)
	Median (IQR)	-0.02 (-0.43-0.6)	0.25 (-0.52-0.57)	-0.05 (-0.19-0.54)

***Lower estimates indicate lower levels for quality of life*

4.5.5 Healthcare resource use

Healthcare resource use utilisation, including medicines and consultations, are presented in **Table 21 and Figure 5.** The mean number of medicines increased slightly at three months (mean, range; 2.8, 1-5) compared with baseline (mean, range; 2.3; 0-4) then decreased at the end of the follow-up (mean, range; 2.3; 0-4); however, the type of medicines was changed over time, in that opioid use was reduced and use of anticonvulsants and antidepressants increased. The use of non-opioid analgesics increased in the three-month period and lowered in the six-month period. Further data about the dosage was not provided by the patients. Healthcare visits, according to data recorded in patients' diaries, were reduced in the period from 4-6 months **(Figure 5)**. In regard with the treatment pathways of the participants, it was difficult to identify these pathways with the small sample size.

Table 21. Utilisation pattern of medicines in FM/CWP patients attending PMS during study period

	Baseline	**Three months**	**Six months**
Mean total medicines (range)	2.3 (0-4)	2.8 (1-5)	2.3 (0-4)
Antidepressants	0.4 (0-1)	0.8 (0-1)	0.4 (0-1)
Anticonvulsants	0.5 (0-1)	0.6 (0-1)	0.6 (0-1)
Opioids	0.9 (0-2)	0.8 (0-2)	0.8 (0-2)
Non-opioids: NSAIDs and paracetamol	1.9 (0-4)	2.3 (1-4)	1.9 (0-3)

NSAIDs Non-steroidal anti-inflammatory drugs

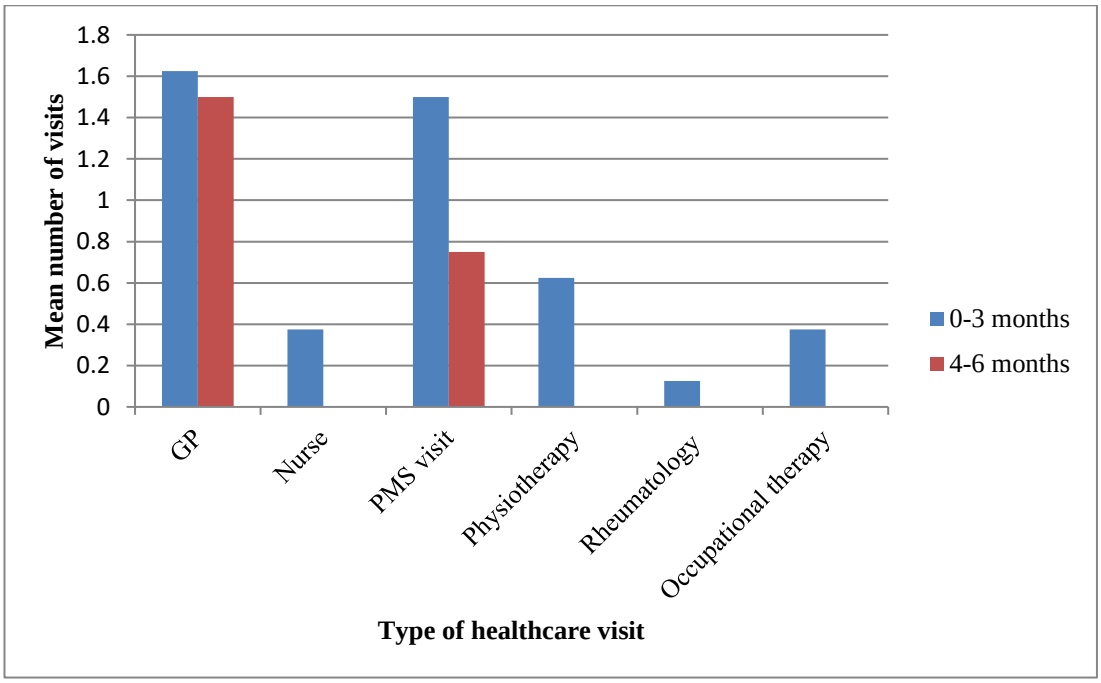


Figure 5. Healthcare resource use per patient during the study period

4.6 Discussion

Although the sample size of this study was small, which affected many aspects of this thesis, including assessing the feasibility of performing a future study of PMS in people with FM/CWP in Nottingham, many points can be extracted and discussed, as listed below.

4.6.1 Recruitment and retention rate

While it was possible to recruit patients to the study, the sample size was small. There were several possible reasons. Firstly, some patients were not eligible under the study inclusion criteria, so they were not invited to take part (the total number of referred patients with FM/CWP was not available in this study). Secondly, there was a seasonal variation effect, in which many patients did not attend their appointments during the summer months, as their FM/CWP symptoms' severity was relieved (Dr. Greg Hobbs, personal communication, July 2017). Thirdly, the annual PMSs' report for the number of referred FM/CWP patients to the PMS in the previous year (2013-2014) may have included patients with other musculoskeletal conditions; therefore, the expected sample size (96 patients per year) for the study may be an overestimate. However, data are not available to support this supposition. Fourthly, the diagnosis of FM/CWP is a challenge for GPs, which can delay the referral (19). Hughes et al. emphasise that the prevalence of diagnosed FM in the UK (0.18%) recorded in the Clinical Practice Research Datalink (CPRD) was considerably lower than in other countries (47). The author stated that the reported cases in the database may reflect more severe cases that have been diagnosed by GPs in the UK. The reluctance of GPs to diagnose conditions

that are poorly defined (147) explains the low prevalence (47), and maybe the small number of patients referred to the PMS.

In the literature, several reasons for small sample sizes have been reported, including fewer eligible patients than estimated prior to performing a trial (148, 149). When designing a study, recruitment estimates, such as the number of patients visiting a clinic per month, have been used widely to estimate the number of participants and the required duration for recruitment as accurately as possible before conducting a trial (148, 149). According to the experience gained in this study, the actual number of referrals was not predictable by estimating the number of patients from previous years' referrals and the feasibility of performing a future study cannot be determined with this sample size.

Three studies found in the literature reported that recruiting and retaining patients with chronic pain is a major difficulty in research (150-152). Although many strategies to improve the recruitment of patients into research studies were adopted at the very beginning of this study, such as reminders and patients' preference for time of contact, the recruitment process was challenging, in which an ethical amendment to the protocol was performed to change the process of obtaining the consent form and provide an inconvenience allowance to patients. These amendments improved the recruitment and maximised the retention of the small sample in the remaining study period.

The sample size of the current study was small and it was not possible to compare the results with other studies, but it was important to note that the attrition rate was 0%

and 20% at three and six months post referral, respectively. Attrition rates with similar interventions and patients were shown to be low in previous research (153). A systematic review found that attrition rates in FM/CWP varied from 14.8% (range 0 to 27%) in multicomponent interventions to 27% (SD 18.9%, range 0 to 67%) in aerobic exercise intervention groups (153). When exploring the data of patients who failed to complete the present study, worse health outcomes were observed at baseline compared with study-completers. This was in line with a study with similar patients referred by GPs to a specialised rheumatology nurse-led diagnostic consultation clinic in an outpatient setting (154). The study found that patients who dropped out at three (31%) and six (42%) months post referral had lower scores in HRQoL at baseline (154). This could introduce an attrition bias and limit the validity of the results.

Given that the current study did not aim to identify barriers to participation, having severe pain was one of the identified reasons behind non-participation of two patients in this study. Evidence found that the multimodal impact of pain on different aspects of physical, psychological, and social wellbeing, limits patients' activity (19, 155) and ultimately results in a lower HRQoL (156). Knowing the wide impact of pain on these patients' lives, this may also impact on participation in research. Given that this study implemented almost all the recommended methods to enhance the recruitment process documented in the literature, it is important to explore the barriers to participation and how to promote study involvement among people with FM/CWP in future research.

4.6.2 Effectiveness and healthcare resource use

The design and the small sample size of this feasibility study do not allow for formal evaluation of the PMS intervention; however, several findings were observed. First, a small improvement was observed in SIQR, BPI and the EQ-5D-3L in the three months data, suggesting that the effect of the PMS intervention involves global health including specific domains in FM/CWP such as pain.

The moderate treatment effect was comparable with the findings of studies with such intervention. For the EQ-5D-3L, improvements of 16% and 1% at three and six months post-referral, respectively, were found in this study. In Kroese et al.'s observational feasibility study (n=100) of individualised PMS interventions in the Netherlands, an 11 % improvement in the EQ-5D-3L at three months was reported (157). Other studies found a range of improvement gain between 1.6 to 5.9% in six months (130). In the SIQR scores, an improvement of approximately 2% was found. This low level of improvement was attributed to the small sample size, as other studies found an improvement of between 15 and 19% (157, 158). The improvement observed from the data at three months was not always sustained to six months. The cause of this effect was not investigated due to the small sample size in the study.

There were some concerns in the study regarding the level of completeness of healthcare resource use diaries among patients, in which patients may have recorded non-FM/CWP visits that overestimated the HRU; however, the data showed that the overall number of visits to healthcare professionals declined through the study period. A similar finding was observed in a RCT of PMS compared with standard care (159);

although the significance was not tested pre- and post-PMS intervention, all numbers of visits decreased.

All the study procedures, including contact with the PMS staff, regular contact with participants in between questionnaires, diary reminders, inconvenience allowance and patients preferred time for contact, might reduce the attrition rate. Although the sample size is small, if this procedure is replicated in a future study with more study sites, it could quantify the actual clinical and economic effect of PMS on people with FM/CWP, and could provide better data to populate the economic model presented in Chapter Five.

4.6.3 Strengths and limitations

The major limitation of this study was the very small sample size. This limitation has an effect on identifying the effectiveness of PMS, and on required data inputs for the decision analysis model in Chapter Five to estimate the cost-effectiveness of PMS in patients with FM/CWP. However, there are known practical difficulties and methodological challenges in trials of complex interventions that require feasibility work prior performing a trial (116). In non-complex interventions, feasibility work also has an essential role in estimating the sample size to achieve the target sample for future studies. In a review of 151 UK public funded RCTs, recruiting between 2004 and 2016 (160), 60% (91/151) of the trials did not perform feasibility work prior to the trial; only 40% (61/151) achieved their original patient recruitment target and 56/151 (37%) achieved <80% of their original target. Of these, 34% (52/151) revised their original target sample size and 32% (41/151) required an extension due to the low

recruitment rate (160). Therefore, one of the major strengths of this study that it has identified key uncertainties and anticipated the recruitment problems that could increase cost and extend or undermine a future trial of Nottingham PMSs for people with FM/CWP.

An additional strength of the study in regard to study procedures was that all study documents, including questionnaires, diaries, the patient information sheet, and the consent form have been reviewed by a patient representative experienced in pain research. Moreover, validated measures were used for each of patients' outcomes. These outcome measures able to assess the effectiveness of the service from the patient perspective in future studies.

When interpreting results in the current study, it should be remembered that these results apply only to patients referred to the Nottingham PMS, with tailored interventions, and cannot be generalised to patients in other settings or to other interventions. The description of the intervention did not follow the TIDieR checklist (137). The lack of a comparable control group also limits the interpretation of PMSs' effectiveness. A final limitation of the exploratory analysis is that, although care was taken to avoid double counting of healthcare resource use, some patients could have reported non-FM related visits as part of the FM related visits. As stated before, this was a feasibility study, so the results on clinical outcomes and HRU should therefore be viewed as only exploratory.

4.6.4 Future recommendations

The results of this study suggest that it is not be possible to perform a future trial on PMSs in managing people with FM/CWP without first considering some key points arising from this work. Firstly, future studies should include more PMSs, to recruit more patients. Secondly, the completeness of the healthcare resource use data was unknown in this study. Studies should consider comparing HRU from diaries with medical records for patients with FM/CWP. Thirdly, qualitative work to identify the facilitators and barriers to participation among people with FM/CWP is highly warranted in future research. Finally, as there were many challenges in the recruitment and retention of the participants in the study, the results could also be affected by the attrition bias; thus, in future studies, exploring different strategies to recruit and retain patients with chronic pain, especially severe pain, is important.

4.7 Conclusion

In summary, this observational single-arm study in patients with FM/CWP referred to PMSs assessed the feasibility of the study's procedures, and recruitment and retention rates to the study. It also identified the characteristics of the FM/CWP patients, and assessed the effectiveness and HRU during the six-month follow-up period. Although a small sample was recruited to the study, the study methods and findings provide insights regarding the challenges and best practice to be used to enhance recruitment and retain individuals with FM/CWP in a research study. The aim of this PhD is to conduct a programme of feasibility work in preparation for the conduct of a definitive RCT of PMSs to manage people with FM/CWP. Applying the recommendations of

this study before performing a future RCT regarding the cost-effectiveness of PMSs to manage people with FM/CWP is highly important in order to avoid the costs of trial extensions or failures.

The aim of the next chapter is to evaluate the indicative cost-effectiveness of PMS using economic modelling. Due to the small sample size and lack of a comparator group in this study, some estimates from this chapter were combined with other published estimates obtained from the systematic review performed in the previous chapter (Chapter Three) and other resources, in order to populate the model and derive an indicative economic evaluation of PMS as a way to manage FM/CWP, compared with SC. Further details are discussed in Chapter Five.

Chapter 5: The indicative cost-effectiveness of PMSs compared with standard care in the management of FM/CWP- a Markov decision analytic model

5.1 Introduction

The assessment of cost-effectiveness of a service such as the PMS is an essential component in determining whether a service is approved for funding or rolled out beyond initial pilot sites. The systematic review (Chapter Three) showed that methodological weakness in the published economic studies of PMSs for FM/CWP limits conclusions about the cost-effectiveness of these services. The lack of evidence regarding the cost-effectiveness of the PMS prevents decision makers charged with resource allocation from agreeing on the most effective management pathway in managing FM/CWP patients. As the PMS utilises a range of healthcare professionals working in a team, one implication may be increased cost to the NHS. However, better clinical outcomes may improve pain, functioning, and quality of life, which may have an impact on healthcare utilisation. Therefore, the main aim of the work described in this chapter is to assess the cost-effectiveness of PMSs in Nottingham compared with SC in managing people with FM/CWP.

Following the recommendation of the MRC (116), the indicative economic evaluation presented in this chapter was performed using data obtained from the feasibility study in Chapter Four and complemented with published data from Chapter Three and other literature. This chapter describes the methods used to build and structure a decision analytic model, and present results of the cost-effectiveness of a PMS compared to SC in managing people with FM/CWP.

5.2 Objectives

The objectives of this chapter are to:

1- Develop an economic model that represents the treatment pathways associated with the management of FM\CWP through the PMS or SC.
2- Populate the treatment pathway model with relevant probabilities, utilities, and cost.
3- Identify and quantify the incremental costs of the PMS strategy compared with SC.
4- To identify and quantify the incremental benefits of the PMS strategy compared with SC.
5- Analyse the incremental costs per the incremental benefits of the PMS strategy compared with SC.
6- Identify and quantify the uncertainty around the incremental costs and benefits of the PMS strategy compared with SC.

5.3 Methods

The economic evaluation of the PMS compared with SC in managing FM/CWP was carried out using a Markov modelling approach. This evaluation adhered to best modelling practice as outlined by CHEERS, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines, and the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) criteria (123, 161-163).

5.3.1 The Nottingham pain management service and the standard care pathway

No published literature was identified that has described treatment pathways for pain management services in Nottingham, or other non-PMS approaches, referred to here as "standard care (SC)", for the management of FM/CWP in the UK in general, or the

Nottingham SC in particular. Therefore, it was necessary to characterise the treatment pathways for the two comparators under investigation in this study, namely the Nottingham PMS and SC pathways. The best method for characterising treatment pathways is direct observation of a sample of people undergoing both comparators. When this is not possible, it is necessary to rely on expert opinion and practitioners' account of the treatment pathway.

The direct observation of referred individuals with FM/CWP to PMS (described in Chapter Four) was insufficient, due to the limitation in the sample size (n=10). In addition, based on GPs meetings, data regarding the SC treatment pathways was not possible to obtain it due to the difficulty in identifying those patients in the SC practice. Therefore, meetings with general practitioners who worked in collaboration with Nottingham's PMS and aware about the SC practice was the only way to obtain details of management pathways. Three GPs were interviewed. The first contact was with Dr. Kelvin Lim (clinical lead of the primary integrated community services in Nottingham) who recommend me to contact two other GPs: Dr. Kerri Sallis (general practitioner at Balderton Primary Care Centre, Newark, Nottingham) and Dr. Nicole Atkinson (general practitioner at Church Street Medical Centre, Eastwood, Nottingham). These GPs were familiar with the SC pathway i.e. before the establishment of PMS, and the new pathway, the PMS. The purpose of this interview was to gather information regarding the types of treatment provided, their duration, and criteria for referral to secondary care and to the PMS. Details of both pathways are described below.

5.3.1.1 The community pain management service pathway

The PMS is a service targeting patients with pain in a community setting who have been treated by their GP but not achieved the intended level of pain relief, functionality, and quality of life. It was reported that the time to refer the patients to the PMS is not fixed and it depends on each patient's case (Kelvin Lim and Katie Sallis, personal communication, November 9, 2016). Unless the patient presented to his/her GP with red flag indicators such as thyroid problems, systematic malaise with weight loss, or involvement of joints, a referral to the secondary care is indicated. An outline of the PMS pathway is presented in **Figure 6.**

Upon referral of patients to the PMS by their GPs, patients are triaged by the pain consultant and may have further investigations and consultations with members of the team (including a pain consultant, a physiotherapist, a biopsychosocial practitioner, and a nurse) for supported self-care management, or community services such as physiotherapy, or more specialist secondary care services such as rheumatologist (115). The PMS facilitates access to a wide range of diagnostic and treatment pathways, such as MRI, rehabilitation programmes, and minor procedures such as trigger point injections. The management of the PMS is not a pre-fixed programme where all patients with a certain diagnosis have the same programme. Instead, an individualised treatment plan is prescribed according to patients' needs.

Once all investigations are carried out and a treatment plan is ready, the patient will be referred back to his/her GP and followed up via telephone calls from the PMS every six months. People with rheumatological symptoms such as arthritis or SLE will be

referred to a rheumatologist in secondary care for further investigations and management (Kelvin Lim and Katie Sallis, personal communication, November 9, 2016).

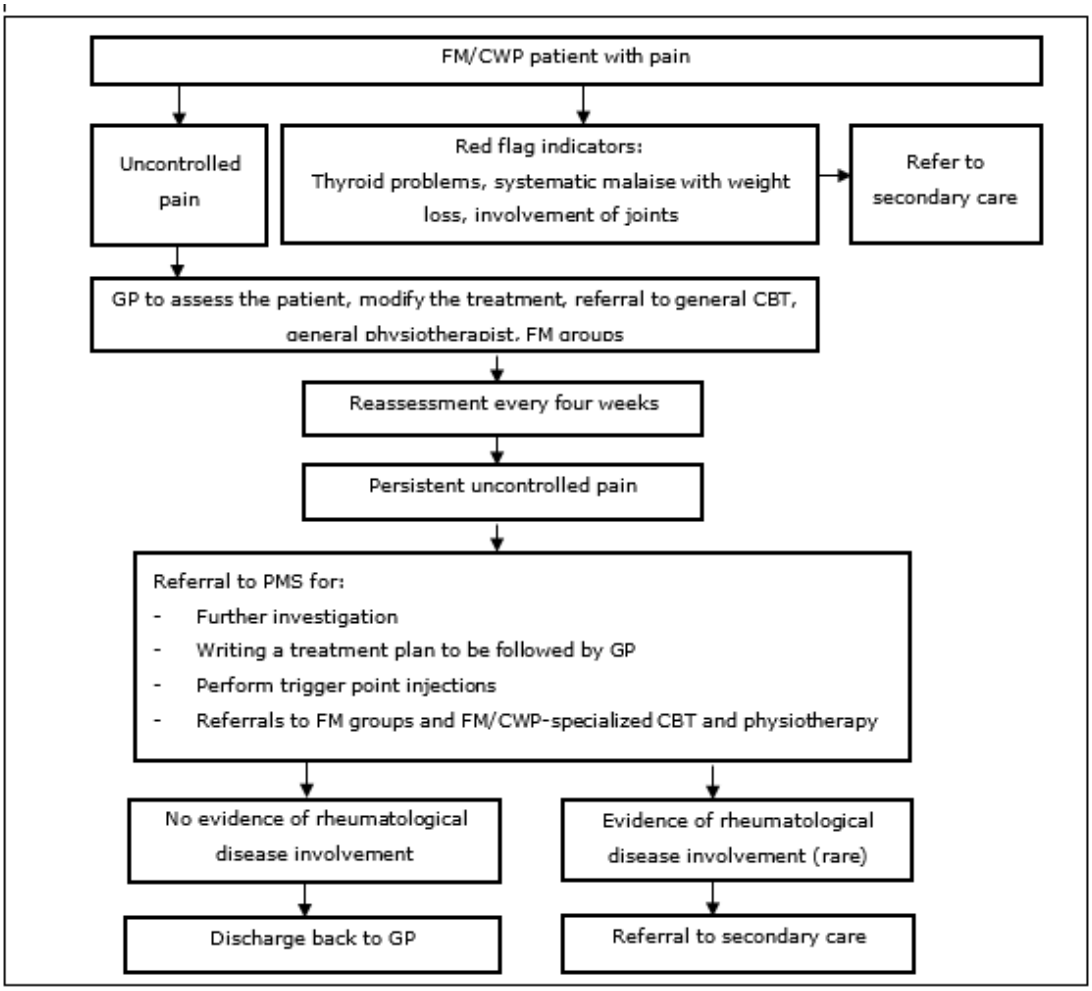


Figure 6. Pain management service pathway, based on the interviews with GPs

5.3.1.2 Standard care pathway

In the standard care pathway, patients are referred to secondary care if the intended outcomes of pain relief, functionality and quality of life are not achieved. An outline of the SC pathway is presented in **Figure 7.**

Before establishing the PMS, patients with FM or CWP were treated initially by their GPs. If treatment failed to improve patients' outcomes, then referrals to physiotherapy, pain medicine or rheumatology in secondary care were considered. Once the patients had been reviewed by secondary care specialists, the patients were followed up by his/her GP (Kelvin Lim, Katie Sallis, and Nicole Atkinson, personal communication, November 9, 2016).

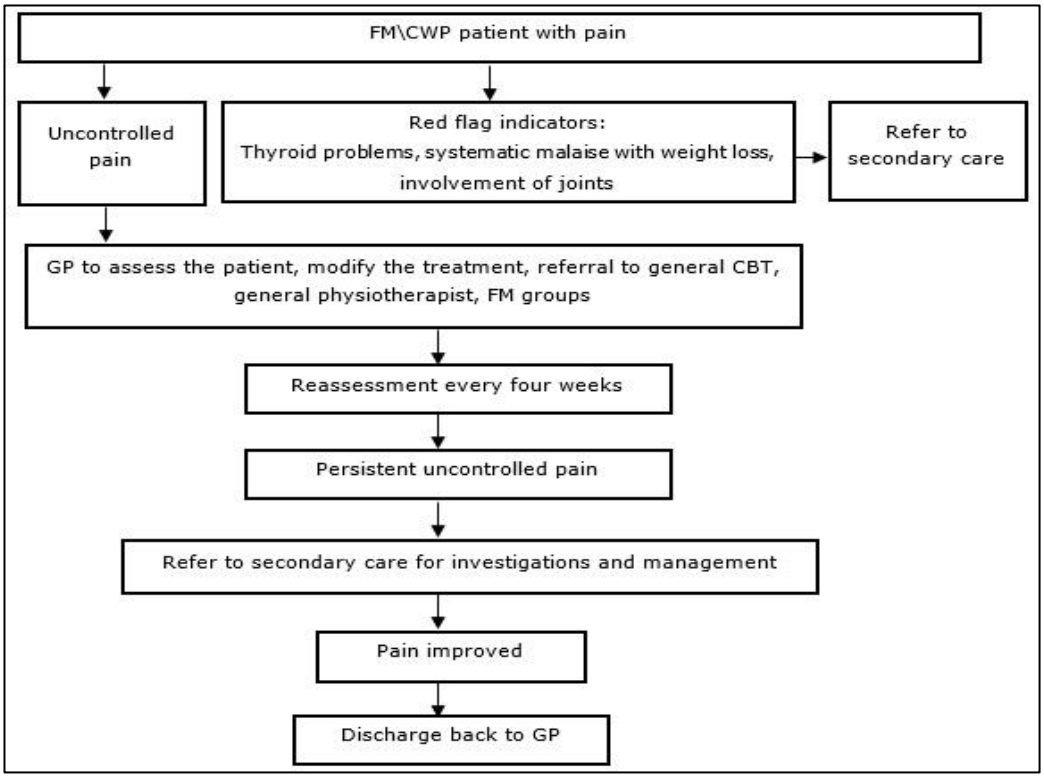


Figure 7. Standard care pathway, based on the interviews with GPs

5.3.2 The decision-analytic model

5.3.2.1 Selection and justification for the decision-analytic model

In designing a decision-analytic model, the type of model has to reflect the natural history of the condition and represent the impact of any intervention on that condition. In FM/CWP, the model should reflect the future consequences i.e. functionality and quality of life of patients with these conditions and the impact of interventions i.e. PMS and SC on patients' functionality and quality of life and associated resource use.

In this evaluation, the Markov model approach was chosen over a simple decision tree in structuring the FM/CWP model mainly because a Markov model is able to handle the multiplicity of possible consequences that can occur in a decision tree and which limit the number of possible pathways thereafter (164).

Discrete event simulation (DES) is another type of decision analysis model. It depends on the interactions between individuals, populations, and/or their environment. One of the limitations of DES is the requirement of data to populate the regression model (164). Therefore, a Markov model was considered the more appropriate modelling approach to simulate the clinical course of FM/CWP.

The economic model consisted of a decision tree reflecting treatment choice (CPC vs SC) followed by a Markov model to describe the possible health states of patients treated in the PMS or SC. In the decision tree, the cohort with FM/CWP undergoes either PMS or SC. Identical Markov models follow on from each of these branches. A Markov model with a set of possible transition probabilities between FM/CWP health

states over a series of fixed cycles (see section 1.5) was designed to reflect as closely as possible the natural history of the disease and the possible consequences of interventions.

5.3.2.2 Markov model structure

Clinically, as described in the literature review chapter (Chapter Two), FM and CWS are more than just a pain syndrome. Numerous symptoms affect patients, such as fatigue, sleep disturbance, mood disturbance, cognitive dysfunction, depression and anxiety. These symptoms affect the patients for their life time and all available management strategies just alleviate the severity of the symptoms without curing the condition.

This multidimensional nature of FM/CWP necessitates the global and integrated assessment of its symptoms as one entity over time. Assessment based on pain alone will not capture all other aspects of patients' concerns, such as the ability to maintain functionality or return to work. Therefore, the health states of the Markov model should be based on the severity of the FM/CWP overall symptoms, beyond just looking at pain.

The systematic review in Chapter Three did not identify any studies using decision analytic models in FM/CWP. As the search strategy for the previous systematic review was restricted to PMS interventions, a broader literature search was performed including the search term "fibromyalgia", or "chronic widespread pain", and "Markov model", or "decision analysis model". Three cost-effectiveness studies of pharmacological interventions (duloxetine, pregabalin, all pharmacological

interventions) in FM/CWP based on Markov decision analytic models were identified (165-167). The economic evaluations were performed with a three-month cycle length and two-year time horizon (165-167). The perspectives were from those of the UK NHS(165), the Mexican Public Health System (166), and the US health care payer (167). All models in the three studies were based on pain severity, which reflects one element of FM/CWP. As stated above, pain severity alone does not reflect the multidimensional nature of FM/CWP symptoms. Therefore, a de novo model was built in this PhD to reflect the nature of FM/CWP, as explained in this chapter.

As mentioned previously in the literature review chapter, the FIQR is the most recommended outcome measure in FM/CWP by OMERACT (61). It is able to measure all symptoms in FM/CWP including pain in which it reflects the complex nature of FM/CWP more than pain alone in previous studies (165-167). **Figure 8** shows a schematic representation of the decision analytic model. The model structure is built as a standard decision tree followed by a Markov model, using TreeAge Pro 2015 (168). The health states were defined according to the FIQR severity score: mild (0-38), moderate (39-58), and severe fibromyalgia (59-100) (62). An additional absorbing health state represents ‘dead’, which the cohort can enter from all health states at any time.

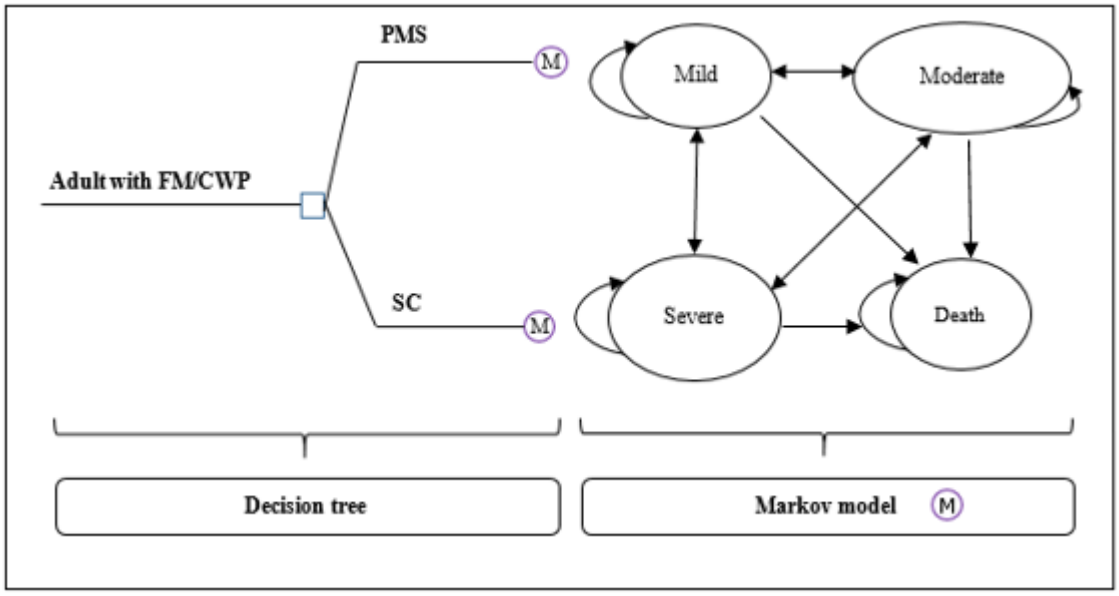


Figure 8. Model structure, health stated based on the FIQR severity level

As described previously in literature review chapter (Chapter Two), many studies have found that FM/CWP itself is not reported as a leading cause of death (24, 31). However, studies have found that depression (25, 26), chronic pain (27, 28), and sleep disturbance (29, 30) are risk factors for suicidal ideation and suicidal attempts. These three different factors are cardinal symptoms in FM, and an association between FM/CWP and suicide has been found (23, 31, 169). Calandre and colleagues found a significant relationship between risk of suicide and FIQR severity level ($p<0.0001$), indicating that higher FM severity patients are at higher risk of suicide (32). In this model, it was assumed that patients with severe FM are at a higher risk of suicide and this was incorporated into transition probabilities to death. Therefore, the probability of transitioning to the dead state combines risk of suicide with age-adjusted all-cause mortality rates.

The arrows on the Markov diagram indicate the transitions patients can make in the model. The transition probabilities governing the direction between health states in the model are explained in section 5.3.4. Within one cycle (cycle length set as 3 months, section 5.3.4.1), the patient can remain in the same state, move to a lower, to a higher severity state, or die. Patients who enter the dead state will remain in this state (absorbing state).

5.3.3 Population and initial distribution

The age of population included for the analysis reflected the patients identified in the feasibility study (Chapter Four). Subjects in the cohort were adults (18 years or older) with a diagnosis of FM or CWP. The mean age (SD) of the cohort was 41 (9.88) years. Due to the limited funding in this PhD, an extraction of age data for FM/CWP patients referred to PMSs from the database was not possible. As the sample size of the cohort in the Chapter Four was small (n=10), a literature search for RCTs, longitudinal studies and reviews was performed. However, no evidence was found to support the initial distribution from which people transition between the health states for standard care or PMS type intervention. Therefore, authors of potentially suitable studies were contacted to provide the datasets of their published studies in order to obtain initial distribution and derive the transition probabilities (section 5.3.4) of both PMS and SC pathways based on FM/CWP severity.

After communicating with potentially suitable authors, Luciano and colleagues responded and agreed to provide the data (128). The dataset obtained was for 216 primary care patients meeting the ACR criteria for FM/CWP recruited in a twelve-

month RCT of a pain management service compared with a control group receiving standard care in Spain (128). The intervention was provided by rheumatologists and a clinical psychologist and consisted of educational sessions, autogenic training (exercises and relaxation techniques), in addition to medical management provided by the GP (128). The PMS in Nottingham provides similar services to the intervention under evaluation by Luciano et al (section 5.3.1.1 and 5.3.1.2): physical training, educational sessions, and cognitive behaviour therapy were provided with a treatment plan written by the pain consultant for the GP. The difference between the two PMS interventions was that the treatment plan in Nottingham is individualised to patient's specific needs while the intervention under evaluation by Luciano et al. provided a pre-structured programme. Tailored PMS is recommended (6, 170-172) and considered to be more effective than a pre-structured PMS such as in Luciano et al.'s intervention. Nevertheless, the intervention in Luciano et al. is comparable to Nottingham's PMS settings and was the only source of available data.

For standard care, health care pathways in Spain are similar to those in the UK (173, 174). GPs in both countries act as gate-keepers for secondary care specialists and community-based health services (section 1.2). Therefore, the intervention and control arm in the Luciano study represent the PMS and SC in this study, respectively.

The dataset obtained for the analysis contained demographic data and FIQR results at baseline, post-treatment (2 months), and 12 months, for both intervention and control group. STATA 14 (142) was used to analyse the dataset and determine the initial distribution of the population and transition probabilities (section 5.3.4). The initial

distribution of patients in Luciano and others study (n=216) was 112 patients (51.9%) with severe , 86 (39.8%) with moderate, and 18 (8.33%) with mild FM/CWP (128).

5.3.4 Transition probabilities

Patient progression is determined by simulating the movement of the cohort through health states, starting with the patient's presentation with severe, moderate, or mild FM/CWP in cycle 0; patients then are assigned into other health states based on the probability of the event occurring in the next cycle - this is the transition probability associated with the event.

As reported previously, in section 5.3.3, the sample size of the cohort in Chapter Four was unable to derive data regarding the transition probabilities in PMS. Therefore, dataset provided by Luciano and colleagues was used to derive the required transition probabilities (128). **Table 22** represents the preliminary transition probabilities for two and twelve months for both arms. In order to use this data in the decision model, transition probabilities were transformed to match the cycle length in the present study. The next section (section 5.3.4.1) describes how these data were transformed to three-month transition probabilities to be used in the economic evaluation.

Table 22. Two- and twelve- months transition probabilities for FM/CWP patients receiving PMS and SC in Luciano et al study (128).

Baseline (n)	n (**probability**)		
	Severe	Moderate	Mild
Transition probabilities for PMS from two months data			
Severe (63)	31 (**0.492**)	24 (**0.381**)	8 (**0.127**)
Moderate (37)	1 (**0.027**)	15 (**0.405**)	21 (**0.568**)
Mild (8)	0 (**0**)	1 (**0.125**)	7 (**0.875**)
Transition probabilities for SC from two months data			
Severe (49)	31 (**0.632**)	17 (**0.347**)	1 (**0.201**)
Moderate (49)	15 (**0.306**)	25 (**0.510**)	9 (**0.184**)
Mild (10)	2 (**0.20**)	3 (**0.30**)	5 (**0.50**)
Transition probabilities for PMS from twelve months data			
Severe (63)	29 (**0.460**)	25 (**0.367**)	9 (**0.143**)
Moderate (37)	6 (**0.162)**	11 (**0.297**)	20 (**0.541**)
Mild (8)	0 (**0**)	2 (**0.25**)	6 (**0.75**)
Transition probabilities for SC from twelve months data			
Severe (49)	28 (**0.571**)	18 (**0.367**)	3 (**0.061**)
Moderate (49)	17 (**0.347**)	24 (**0.49**)	8 (**0.163**)
Mild (10)	2 (**0.20**)	2 (**0.20**)	6 (**0.60**)

5.3.4.1 Cycle length and time horizon

The cycle length and time horizon usually depend on the nature of the condition and the intervention, respectively. A three-month cycle length was used for the regular transition calculation, in accordance with the primary response assessment point used in many decision analysis models in fibromyalgia (section 5.3.2.2) (165-167), and in line with clinical practice where a three-month period is adequate to detect an effect for any intervention in FM/CWP (personal communication: Kelvin Lim, November 2016). A lifetime horizon (until 100 years of age) was performed to test the cost-effectiveness of PMS until all patients exited the model.

As the study performed by Luciano 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, 3-month probabilities are calculated. The rate is derived from transition probabilities, then the rate is converted into probabilities for the period of interest, i.e. three months, using the equation below (175):

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

$$p = 1 - exp^{\{-r*t\}}$$

where *p* is the probability, *r* is the rate and *t* is the time period of interest. Using equations 1 and 2, the three-month transition probabilities (**Table 23**) for both arms were calculated using the two-month and twelve-months data for both arms. The twelve-month probabilities were chosen, because they will not overestimate the

effectiveness of PMS. The two-month probabilities were tested in the sensitivity analysis.

Table 23. Calculated three-month transition probabilities from two- and twelve-months probabilities for the PMS and SC pathways

Markov transition probabilities	PMS	SC
From twelve-month probabilities (base case)		
Severe to severe	1-(0.763+0.335) = 0.098	1-(0.721+0.059) = 0.22
Severe to moderate	0.763	0.721
Severe to mild	0.335	0.059
Moderate to severe	0.079	0.666
Moderate to moderate	1-(0.079+0.919) = 0.002	1-(0.666+0.456) = 0
Moderate to mild	0.919	0.456
Mild to severe	0	0.400
Mild to moderate	0.330	0.600
Mild to mild	1-(0+0.330) = 0.67	1-(0.600+0.400) = 0
From two-month probabilities (sensitivity analysis)		
Severe to severe	1-(0.513+0.184) = 0.303	1-(0.472+0.030) = 0.498
Severe to moderate	0.513	0.472
Severe to mild	0.184	0.030
Moderate to severe	0.040	0.422
Moderate to moderate	1-(0.040+0.716) = 0.244	1-(0.422+0.262) = 0.316
Moderate to mild	0.716	0.262
Mild to severe	0	0.284
Mild to moderate	0.182	0.414
Mild to mild	1-(0+0.182) = 0.818	1-(0.284+0.414) = 0.302

5.3.4.2 Age-adjusted all-cause mortality rates and suicide

Data regarding age-adjusted all-cause mortality rates were obtained from the Office for National Statistics in the UK for the latest available years (2014-2016) (**Error! Reference source not found.**) (176). These data were 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, as presented in **Table 24**.

Table 24. Age-adjusted all-cause mortality rates in the United Kingdom*

Age	Mortality rate		Age	Mortality rate	
	Males	Females		Males	Females
41	0.001659	0.000949	71	0.021560	0.014339
42	0.001777	0.001076	72	0.024752	0.016116
43	0.001854	0.001161	73	0.026989	0.018277
44	0.002066	0.001277	74	0.030317	0.020312
45	0.002246	0.001394	75	0.033059	0.022436
46	0.002378	0.001479	76	0.036408	0.025071
47	0.002560	0.001611	77	0.040036	0.027839
48	0.002688	0.001747	78	0.044791	0.030916
49	0.003004	0.001902	79	0.049452	0.035425
50	0.003221	0.002163	80	0.056456	0.040553
51	0.003463	0.002308	81	0.062516	0.045640
52	0.003701	0.002526	82	0.071221	0.051959
53	0.004033	0.002795	83	0.079521	0.058719
54	0.004489	0.002995	84	0.088508	0.067531
55	0.004868	0.003362	85	0.100377	0.076003
56	0.005348	0.003623	86	0.111092	0.085465
57	0.005981	0.004000	87	0.123569	0.097278
58	0.006580	0.004241	88	0.138366	0.108463
59	0.007286	0.004695	89	0.152513	0.122870
60	0.008077	0.005234	90	0.168240	0.138451
61	0.008721	0.005719	91	0.183834	0.152324
62	0.009593	0.006210	92	0.205371	0.170413
63	0.010487	0.006801	93	0.227692	0.191161
64	0.011469	0.007308	94	0.241665	0.209367
65	0.012331	0.007988	95	0.264271	0.226339
66	0.013051	0.008481	96	0.278605	0.244355
67	0.014401	0.009481	97	0.305800	0.268462
68	0.015802	0.010672	98	0.334140	0.292079
69	0.017813	0.011647	99	0.351375	0.317580
70	0.019495	0.013015	100	0.381118	0.335497

*Source: National life tables based on data for the years 2014-2016, United Kingdom (176)

The literature regarding the standardised mortality ratio (SMR) of suicide was previously discussed in the literature review (Chapter Two). Dreyer et al. found an SMR of 6.5 (95 % CI; 1.8–16.7) in the FM/CWP population aged 19 to 70 years, compared with the general population (23). Wolfe et al. found that the SMR for suicide in FM/CWP was 3.31, 95% CI= 2.15-5.11 (24) when compared with the general population; however, Wolfe et al. suggest that the SMR was underestimated by the inaccurate coding of some suicidal cases in the records to "accidental death" and it might be closer to 4 if 20% of accidents were misattributed. Both studies demonstrated an increase in the SMR of suicide in patients with FM/CWP. Furthermore, a significant relationship between risk of suicide and FIQR severity level ($r=0.6768$, $p<0.0001$) was observed (32), indicating that higher FM severity patients are at higher risk of suicide.

Based on the previous literature , it was assumed that patients with severe FM/CWP and aged less than 71 years are at increased risk of suicide with an SMR of 6.5 compared with general population (23, 32). In the sensitivity analysis, an SMR ranging from 1.8 to 16.7 was used to represent the uncertainty in the suicide risk (23). To reflect the increased risk of suicide in patients with severe FM, the age-adjusted all-cause mortality rate was multiplied by the suicide SMR to model the increased relative risk. **Table 25** represents probabilities after incorporating death into the model.

Table 25. Revised transition probability matrix for PMS and SC where transitions to dead state vary with the age of the patients.

Markov transition probabilities	PMS	Standard care	Source
Severe to severe	1-(0.763+0.335+[P(death, age) *SMR suicide])	1-(0.721+0.059+[P(death, age) *SMR suicide])	(23, 128, 176)
Severe to moderate	0.763	0.721	(128)
Severe to mild	0.335	0.059	(128)
Severe to death	P (death, age)*SMR suicide	P (death, age) *SMR suicide	(23, 176)
Moderate to severe	0.079	0.666	(128)
Moderate to moderate	1-(0.079+0.919+P(death, age))	1-(0.666+0.456+P(death, age))	(128)
Moderate to mild	0.919	0.456	(128)
Moderate to death	P (death, age)	P (death, age)	(176)
Mild to severe	0	0.400	(128)
Mild to moderate	0.330	0.600	(128)
Mild to mild	1-(0+0.330+P(death, age))	1-(0.400+0.600+ P(death, age))	(128, 176)
Mild to death	P (death, age)	P (death, age)	(176)
Death to death	1	1	

5.3.5 Healthcare resource use and cost

No published literature was identified that has investigated the use of healthcare resources (HRU) by people with FM/CWP in either SC or PMS pathways in the UK. Therefore, a literature search for data from other countries was performed and data from Spain (128), the USA (177), and pooled results for Germany and France (178) were found (**Table 26**). To investigate whether these estimates reflect the management and treatment pathways of FM/CWP patients in the UK and ensure face validity, these data were discussed with the same general practitioners who provided data regarding the PMS and SC pathways in Nottingham (section 5.3.1).

Table 26. Elicited mean (SD) healthcare resource use per patient by FIQR severity for participants with fibromyalgia in three months from different countries

Type of visit/service	Germany and France (178)			USA (177)			Spain (128)		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
General Practitioner visits	3.8	4	5	5 (5)	2.9 (3.7)	5 (5)	4.3 (5.1)	3.1 (5.2)	3.2 (2.9)
Massage therapist	-	-	-	0.6 (2.7)	0.9 (3.7)	0.2 (0.8)	-	-	-
Physiotherapist	-	-	-	0 (0)	1.5 (4)	1.3 (5.4)	-	-	-
Consultant visit	-	-	-	-	-	-	1.1 (1.2)	1.6 (1.2)	2.3 (2.9)
ER visits	-	-	-	0 (0)	0.1 (0.3)	0.1 (0.4)	0.1 (0.4)	0.31(0.7)	0.6 (1.1)
Medication	-	-	-	1.8 (1)	2.3 (1.5)	2.8 (1.6)	2.3 (1.3)	2.3 (0.9)	2.4 (1.6)
Medical tests	-	-	-	-	-	-	4.5 (5.1)	5.2 (8.8)	3.8 (6.2)

Table 27 represents the validated HRU by GPs for the three-month period, the attached costs, and the cost for mild, moderate, and severe FM/CWP. Costs were constructed using 2015-2016 UK sterling. Direct healthcare unit costs were obtained from the following sources **(Appendix 15)**: costs of treatment interventions and investigations were derived from NHS reference costs (179), costs of health care staff from the Personal Social Services Research Unit (PSSRU) (180), medication costs from the British National Formulary (181). All unit cost estimates prior to the 2016 price year were inflated using the Hospital and Community Health Services (HCHS) pay and prices index (180).

For the PMS intervention cost, an additional initial cost, was added to the model. It was assumed that all patients have a first visit to the pain consultant. Moderate FM/CWP was assumed to have an additional follow-up phone call. Patients with severe FM/CWP were assumed to have another follow-up visit to the pain consultant. Attaching to each visit their corresponding unit costs from the NHS reference cost

Table 27. Estimated health care resource use and cost for three-month period of chronic management, stratified by FM intensity levels*

		Mild FM		Moderate FM		Severe FM	
Type of service	**Unit cost, £**	**Mean HRU\ medication**	**Cost, £**	**Mean HRU\ medication**	**Cost, £**	**Mean HRU\ medication**	**Cost, £**
General Practitioner: surgery consultation	36 (180)	4.05	145.8	3.6	127.8	4.1	147.6
Physiotherapist specific joint	18 (182, 183)	0	0	1.5	27	2.5	45
Consultant visit: Rheumatology	152.1 (184)	0.55	83.7	1.3	197.7	1.9	289
ER visits	148.3 (184)	0.1	14.8	0.955	141.6	0.6	89
Blood test	20 (185)	2.25	45	1.75	35	3	60
CT scan[a]	99 (184)	0	0	0.5	49.5	0.5	49.5
MRI[b]	146 (184)	0	0	1	146	1	146
CBT	52 (180)	0	0	1.25	65	1.75	91
Medication	-	2.3	14	2.5	117.5	3.5	310
Total cost (SD), £			**303.3 (166.4)**		**907.2[c] (252.9)**		**1227.1[d] (282.6)**

** Unit costs are per visit\test. Unit costs are expressed as UK averages in 2016 prices; unit cost estimates prior to 2016 price year were inflated using the Hospital and Community Health Services (HCHS) pay and prices index (180)*

[a] range: £70-£121, reference: NHS reference cost 2015-2016. [b] range: £108-167, reference: NHS reference cost 2015-2016.

[c] Total range when applying a and b: £854.7-939.2. [d] Total range when applying a and b: £1174.6-1259.1

CBT: cognitive behaviour therapy; HRU: Healthcare resource use

2015-2016 (**Appendix 15**) (184), initial costs of £181, £201, and £406were assigned for patients with mild, moderate, and severe FM/CWP, respectively, who were attending PMS intervention.

5.3.6 Utilities

A literature search for studies reporting utilities for FM health states was performed and two studies from France and the US were found (186, 187). Both studies were cross-sectional in design, in which patients were recruited from a primary care setting.

In Perrot and colleagues' study (186), patients over 18 years old with a FM diagnosis confirmed by a rheumatologist or pain specialist, and who had had at least three months of treatment were recruited from 18 primary care settings. The total number of participants was 88, with a mean age of 55.2 years (SD=11.8, range=19-80) and 84.1 % of the sample were females. Forty-three percent had severe FM while 37% and 19% had moderate and mild FM respectively. The authors applied the UK tariff for the valuation of EQ-5D-3L (72) as summarised in **Table 28**.

Table 28. EQ-5D-3L utilities value for fibromyalgia

Study	EQ-5D-3L Utilities	Mean (SD)
Perrot et al. (186)	Severe FM	0.18 (0.33)
	Moderate FM	0.44 (0.27)
	Mild FM	0.65 (0.18)
Schaefer et al. (187)	Severe FM	0.20 (0.31)
	Moderate FM	0.57 (0.21)
	Mild FM	0.76 (0.11)

The trial undertaken by Schaefer et al. was also a cross-sectional study performed in 20 primary care sites in the US. Patients were recruited if they were between 18 and 65 years old, had a FM diagnosis confirmed by a rheumatologist or pain specialist, and had been on a treatment of at least three months. Patients were excluded if they had a concomitant illness unrelated to FM that was likely to confound the assessment of FM, such as osteoarthritis, SLE, or rheumatoid arthritis. The total number of participants was 203 with a mean age of 47.9 years (SD=10.9, range=19-65) and 94.6 % of the sample were females. Sixty-five percent had severe FM while 24% and 10% had moderate and mild FM respectively. The authors applied the US tariff for the valuation of EQ-5D-3L (72) and summarised in **Table 28**. Perrot et al.'s study was used in the base case analysis, as it has the advantage over the US study in using a UK tariff for

valuation of utilities. The robustness of the ICER was tested thereafter using the Schaefer et al.'s utilities, using one-way analysis (OSA).

5.3.7 Assumptions about attrition of effect size

In the model, it did not seem appropriate to assume the effectiveness was maintained for the lifetime of the patient in the PMS. Therefore, the model incorporated an assumption for attrition of PMS effect, in which an annual 20% reduction in the effectiveness of PMS was applied for two consecutive years, specifically the third and fourth year in the model (5% in cycles from 8 to 15, 20% in total) (**Figure 9**). This assumption was adopted from a study that evaluated the cost utility of CBT intervention in people with low back pain, in which an annual 20% reduction of CBT effectiveness was assumed for two years only (188). Any remaining effect at year 4 was carried on until the patient died according to their age related mortality rate and suicide rate, then the patient exited the model.

The choice to implement this effect after the second year was based on a literature search for studies of PMSs' long-term effectiveness (range: 2 to 5 years) in FM/CWP treatment (**Appendix 16**). In summary, the results from Beasley et al. provide good quality data regarding the effectiveness of PMS at a two-year follow-up (131). The authors found that the effect of PMS was maintained at the two-year follow-up. Studies performed with more than two-year follow-ups have low methodological quality. Therefore, the attrition of effect assumption was applied after year two in the model, based on data by Beasley and colleagues (131).

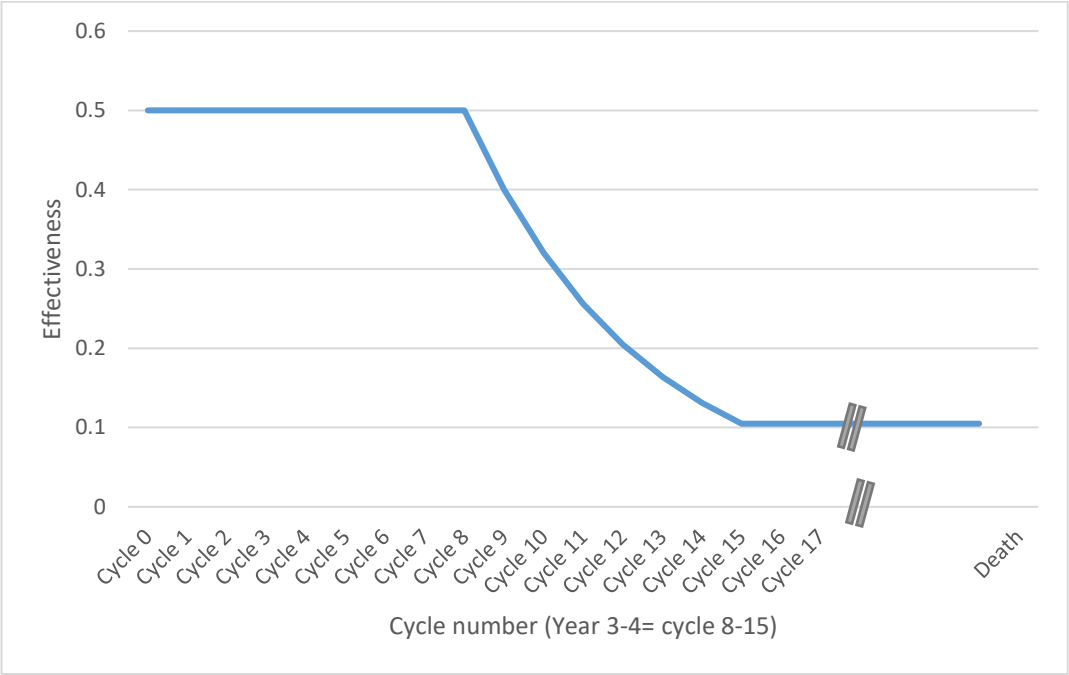


Figure 9. An example for the application of attrition of PMS effect in the base case analysis

5.3.8 Cost-effectiveness analysis

For the analysis, a discount rate of 3.5% for cost and outcomes was applied based on the recommendation of the UK Treasury (189). A half-cycle correction, by assigning half of the reward (190) 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 analysis generated the cost per extra quality-adjusted life-year (QALY) gained by the PMS compared with SC. Deterministic and probabilistic incremental economic analysis were carried out. The incremental cost-effectiveness ratio (ICER), cost per extra QALY generated by PMS over SC, was calculated using the following equation:

$$ICER = (Cost_{PMS} - Cost_{SC}) / (QALY_{PMS} - QALY_{SC})$$

Where available, data were specified as distributions to fully incorporate the uncertainty around parameter values for probabilistic analysis. The analysis was run with 10,000 iterations, using Monte Carlo simulation to obtain point estimates and ranges of QALYs and costs generated by PMS or SC, and ICER distributions.

For the probabilistic sensitivity analysis, each parameter in the model was assigned a distribution, to handle the uncertainty around the data, based on a general approach. For data with values ranging between zero and one and which mutually sum to one, selection of a distribution is highly important to introduce random variation without breaking probability rules. Beta and Dirichlet distributions are the suitable

distributions for categorical binomial and multinomial data, respectively. For example, transition probabilities and initial distribution have more than two categories (mild, moderate, severe, and dead) and Dirichlet distribution was considered the best distribution to handle the uncertainty around the probabilities. For utility values, which are bounded between 0 and 1, beta distribution was assigned. For data that is not bounded to one, such as cost data, gamma distributions were assigned. A summary of all inputs listed from sections 5.3.3 to 5.3.8 and incorporated in the model is shown in **Table 29.**

The proportion of ICER estimates in each of four quadrants of the cost-effectiveness plane was reported. Each quadrant has a different interpretation, as follows(135):

- South-east quadrant (SE) – PMS is less costly and more effective, i.e. PMS should be accepted because it dominates the SC.
- North-east quadrant (NE) - PMS is more costly and more effective. The choice depends on the maximum cost-effectiveness ratio one is willing to accept.
- South-west quadrant (SW) - PMS is less costly and less effective. PMS is recommended if the ICER does not exceed the WTP. The choice depends on the maximum cost-effectiveness ratio one is willing to accept
- North-west quadrant (NW) - PMS is more costly and less effective. PMS should be rejected because it is dominated by the SC.

Table 29. Summary of all Markov model inputs

Model Inputs	Probability/ mean	Source	Distribution
Transition probabilities			
PMS			
Severe to severe	1-(0.763+0.335+[P(death, age) *SMR suicide])		
Severe to moderate	0.763		
Severe to mild	0.335		
Severe to death	P (death, age)*SMR suicide		-
Moderate to severe	0.079	Luciano et al., (128)	
Moderate to moderate	1-(0.079+0.919+P(death, age))		
Moderate to mild	0.919		
Moderate to death	P (death, age)		
Mild to severe	0		
Mild to moderate	0.330		
Mild to mild	1-(0+0.330+P(death, age))		
Mild to death	P (death, age)		
SC			
Severe to severe	1-(0.721+0.059+[P(death, age) *SMR suicide])		
Severe to moderate	0.721		
Severe to mild	0.059		
Severe to death	P (death, age) *SMR suicide		
Moderate to severe	0.666		
Moderate to moderate	1-(0.666+0.456+P(death, age))	Luciano et al., (128)	-
Moderate to mild	0.456		
Moderate to death	P (death, age)		
Mild to severe	0.400		
Mild to moderate	0.600		
Mild to mild	1-(0.400+0.600+ P(death, age))		
Mild to death	P (death, age)		
Cost (SD), £			
Severe	1227 (282.6)	Validated published data by expert opinion	Gamma
Moderate	907.2 (252.9)		
Mild	303.3 (166.4)		
Initial cost of PMS, £		Assumption	-
Severe	406		
Moderate	201		
Mild	181		

Table 29 (continued)

Model Inputs	Probability/ mean	Source	Distribution
Cost (SD), £ Severe Moderate Mild	 1227 (282.6) 907.2 (252.9) 303.3 (166.4)	Validated published data by expert opinion	Gamma
Initial cost of MPS, £ Severe Moderate Mild	 406 201 181	Assumption	-
EQ-5D-3L Utilities, mean (SD) Severe Moderate Mild	 0.18 (0.33) 0.44 (0.27) 0.65 (0.18)	Perrot et al., (186)	Beta
Mean age (range), years	41 (21-55)	Nottingham PMS cohort (Chapter Four)	-
Cycle length	3 months		
Time horizon	Lifetime		
Discount rate	3.5%		

Cost-effectiveness acceptability curves (191) were constructed to express the probability that PMS is cost-effective as a function of the decision-maker's willingness to pay for ICER (WTP) for base case, sensitivity and scenario analysis (192). The currently accepted NICE threshold of £20000 per QALY gained was used to assess cost-effectiveness (193).

Many of the model parameters were subject to 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 one-way sensitivity analysis were chosen conservatively, to incorporate the maximal level of uncertainty around point estimates. 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. Key parameters tested in the OSAs were:

1) Discount rate for cost and outcomes varied between 0-6 percent,

2) Assuming higher cost for the intervention. The cost of an additional visit to the pain consultant for each severity was added and tested,

3) Cost of management of mild, moderate, and severe FM were varied using higher and lower costs in the NHS reference cost (184),

and 4) Utility of mild, moderate, and severe FM from Schaefer et al.'s study (187),

Furthermore, eleven scenario analysis were performed and a probabilistic sensitivity analysis was replicated for each scenario. The first three scenarios tested were for FM severity; these scenarios were done by assuming all patients were at severe, moderate, or mild FM when entering the model. Scenario analysis for five-, twenty-, and forty-year time horizons were also tested against the lifetime time horizon as the base case. An optimistic and pessimistic assumption of the effect of PMS was tested by assuming the absence of attrition of PMS effect and extending the effect of attrition until exponential decay (**Figure 10**). Regarding suicide risk, a scenario was tested by assuming moderate FM/CWP have suicidal risk in addition to the severe cases. Another scenario tested by assuming death is generated only from age-adjusted all-cause mortality rates without suicide risk. A final scenario tested against the base case was when the effectiveness data (transition probabilities) derived from two months effectiveness data from Luciano et al. study (128).

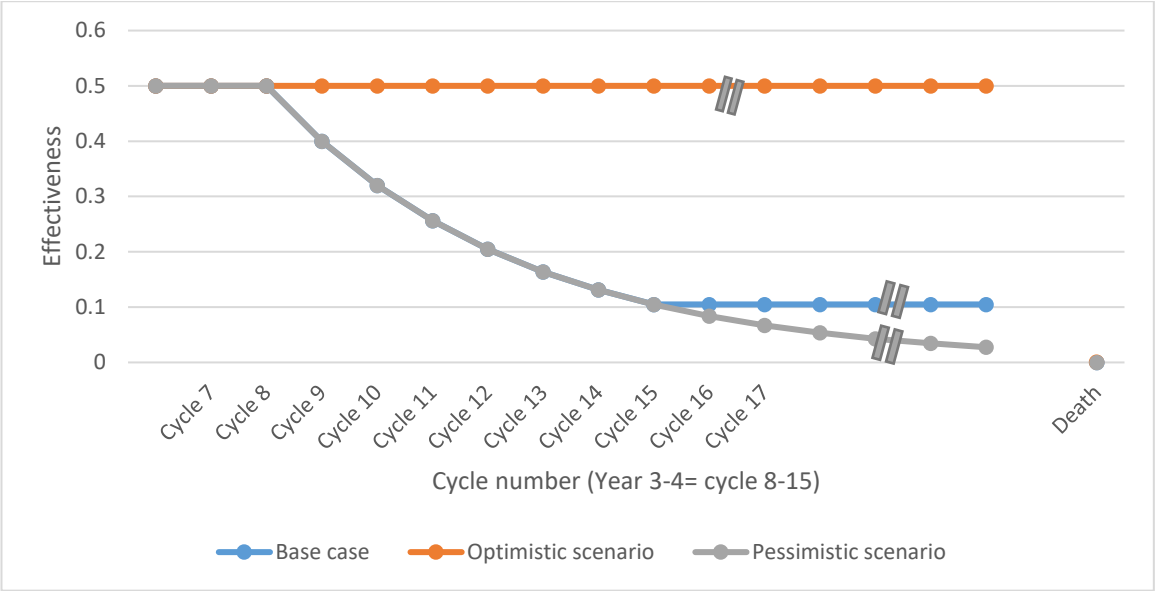


Figure 10. Diagram representing the attrition of PMS effect in the base case, optimistic and pessimistic scenarios

Another way to express the underlying uncertainty is to derive incremental net monetary benefit (INMB) (135), in which all costs and QALYs are measured in terms of monetary units. Results of INMB are appropriate to answer questions about whether or not a health care programme should be implemented or a treatment should be used, rather than which of a number of alternative programmes or treatments is the most efficient (135). INMB is calculated as (135):

INMB= (incremental QALYs x Willingness to pay (WTP)) - incremental cost

A positive INMB implies that the additional value of PMS is more than the extra cost at a given willingness-to-pay threshold, and therefore it should be considered cost-effective. The INMB approach is particularly useful when the ellipse of the ICERs covers the four quadrants of the cost-effectiveness plane (194).

5.3.9 Model validation

The validation of the model followed guidelines recommended by the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) criteria for assessment of the validation status of health economics decision models (163). AdViSHE criteria assess the model's validity by focusing on four main domains: conceptual validation, data validation, computerised model validation and operational validation. The conceptual validation assesses the strength of the theories and assumptions underpinning the model's 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 programs, including the mathematical calculations, are performed according to the model specification. Finally, the operational validation assesses the accuracy and applicability of the model outcomes.

Following the AdViSHE criteria (163), a pharmacy professional (RK) specialising in pain management and also working in the same practice setting was part of the project team providing an insight about the treatment pathways and outcomes used to assess the effectiveness, and provided input regarding whether the model reflected the experiences of patients attending such services in reality. Secondly, the healthcare resource use for patients attending PMSs was discussed with three general practitioners (KL, KS, NA) who worked closely with the service providers. With regard to the computerised model in TreeAge (168), two experienced health economists (GG, LT) provided feedback regarding data inputs, mathematical aspects of the model and analysis of outputs.

Finally, the operational validation of the model outcomes was not possible. as the model presented in this thesis was a de novo model. As reported previously in section 5.3.2.2, other published models in the same disease area were based on pain severity for a two-year time horizon to evaluate the pharmacological interventions (165-167), unlike the current model which takes into consideration the overall impact of FM/CWP, and the chronic nature of the disease through the application of a lifetime time horizon. Therefore, validation of the model relied on feedback from clinical experts and health economics experts at the Universities of Nottingham and Manchester regarding model outcomes.

5.4 Results

The first section in these results reports findings for the base-case deterministic and probabilistic sensitivity analysis of PMS compared with SC management for patients with FM\CWP. Total cost, QALYs, ICERs, and the INMB accrued by treatment pathways are reported. The two following sections report the deterministic sensitivity analysis, including one-way and scenario analysis.

5.4.1 Base case deterministic and probabilistic sensitivity analysis

Table 30 summarises the cost and QALYs accrued by treatment pathways, and resultant ICERs and INMB. In the deterministic analysis, the PMS was the favoured strategy, with a mean lifetime cost per patient of £36209.8 and mean QALYs of 34.8, when compared with a mean cost of £46642.8 and QALYs of 19.6 for SC. The incremental cost and QALYs were £-10433 and 15.2, respectively. The incremental net monetary benefit generated a mean of £314199.2 at WTP threshold of £20000/QALY.

Table 30. Summary of ICERs generated for base-case deterministic and probabilistic incremental analysis of PMS versus SC

Strategy	Cost (£)	Incremental cost (£), PMS vs. SC	QALY	Incremental QALY, PMS vs. SC	ICER (£/QALY)	INMB
Deterministic analysis, mean						
PMS	36209.8	- 10433	34.8	15.2	686.9, PMS is Dominant	314199.2
SC	46642.8		19.6			
Probabilistic sensitivity analysis, mean (2.5% and 97.5% percentiles)						
PMS	35163.2 (16245.2, 57878.8)	-11148.8 (-31420.2, 3494.5)	35.2 (15.2, 57.8)	14.8 (-1.7, 33)	723.4* (-5053.1, 2341), PMS is Dominant	313766.6
SC	46311.9 (23064.6, 70190.4)		20.4 (5.6, 44.2)			

** The proportion of ICER estimates in each of four quadrants of the cost-effectiveness plane: SC dominated by PMS (SE quadrant): 87% (superior), SW quadrant: 3.2 %, NE quadrant: 9.3 %. PMS dominated by SC (NW quadrant): 0.5% (inferior)*

For the probabilistic cost-effectiveness analysis, the mean lifetime cost per patient (2.5%, and 97.5% percentiles) was £35163.2 (£16245.2, £57878.8) for PMS and £46311.9 (£12064.6, £57878.8) for SC. The mean QALYs generated per patient (2.5% and 97.5% percentiles) were 35.2 (15.2, 57.8) for PMS and 20.4 (5.6, 44.2) for SC. Incremental cost and QALYs were £ -11148.8 (-£31420.2, £3494.5) and 14.8 (-1.7, 33), respectively. The resultant ICERs were similar to the deterministic base case, in which PMS was both cost-saving and more effective than SC, with a mean ICER of £723.4 per QALY gained for PMS versus SC (2.5% percentile -5053.1; 97.5% percentile 2341) (**Table 30**).

The incremental cost-effectiveness plane in **Figure 11** shows that there was an 89.2% probability that PMS dominated SC (SE quadrant), with approximately 97 % probability of being cost-effective (with 87%, 9.3%, 3.2% and 0.5% of ICERS located in the SE, NE, SW and NW quadrant, respectively) over a lifetime time horizon at the UK WTP threshold of £20000/QALY **(Figure 12)**. The incremental net monetary benefit generated a mean of £314199.2 at WTP threshold of £20000/QALY.

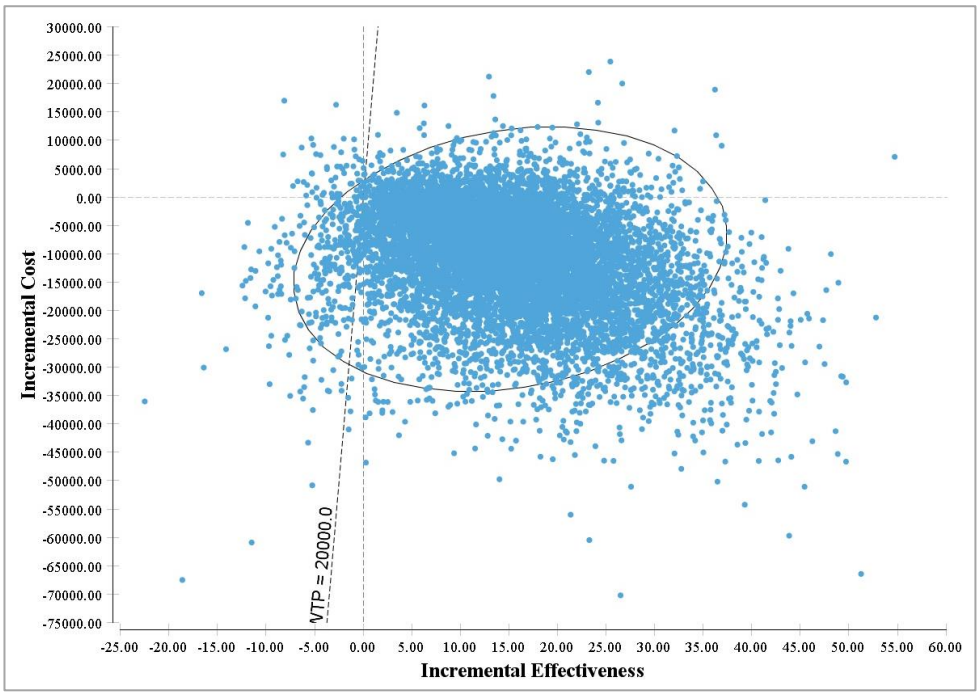


Figure 11. Incremental economic analysis of PMS intervention versus SC

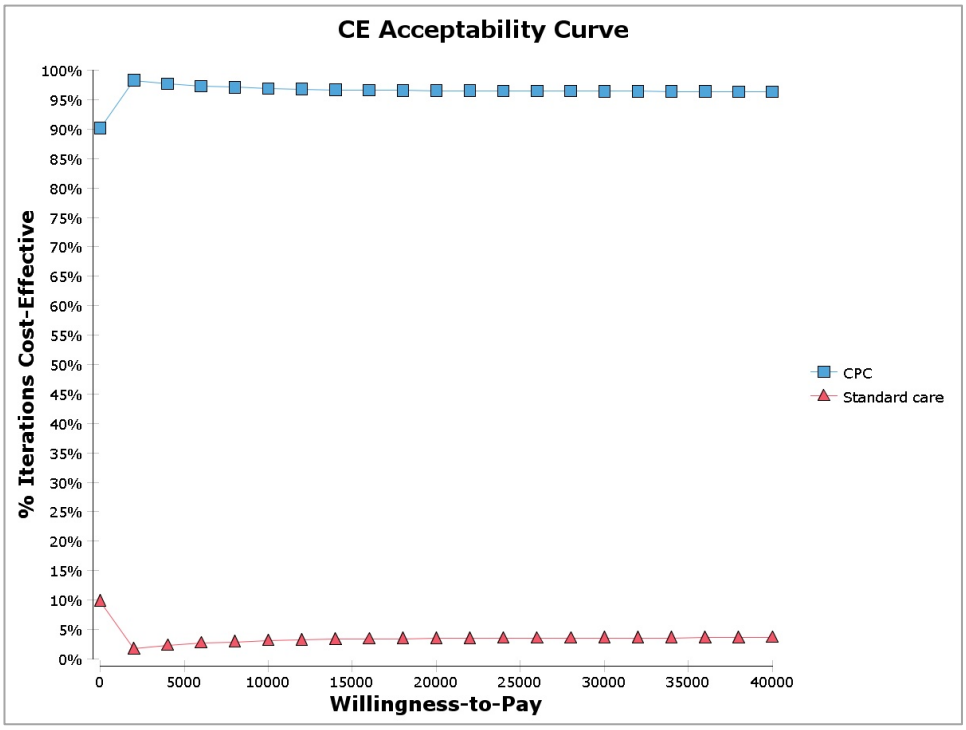


Figure 12. Cost effectiveness acceptability curve of PMS intervention versus SC

5.4.2 One-way sensitivity analysis

A series of OSAs were conducted. **Table 31** presents the alternative values, source of values, and the resultant ICERs and **Figure 13** presents the results in a Tornado diagram. The two parameters with the highest impact on the ICER were 1) altering the annual discount rate, and 2) varying the utility of mild FM/CWP to the value reported in Schaefer et al. (187). The ICERs were not significantly affected by varying the mild and moderate pain utility scores, using the lower and higher unit costs for healthcare resource use, or assuming an additional follow-up visit for patients with FM/CWP.

Altering the discount rate resulted in the highest impact on the ICERs. With 0% discount rate, PMS was still the favoured strategy over SC, with less cost-saving (£-10834.6) and greater benefit (27.3 QALYs) compared with the 3.5% discount rate in the base case (£-10433 and 15.19 QALYs). In contrast, a higher discount rate of 6% resulted in lower total generated QALYs and greater cost-saving (10.9 QALYs and £-9470.3) compared with the base case analysis.

Results generated from varying the utility of mild FM/CWP from 0.65 in the base case to 0.76, which was reported by Schaefer et al. (187), showed that PMS was favoured over SC with a greater total generated QALYs of 18.3 QALYs and cost-saving of £-10433 compared with base case analysis (**Table 31**).

Table 31. One-way sensitivity analysis for cost-effectiveness of PMS compared with SC in FM\CWP patients

Parameter	Alternative values	Comment / source	Incremental cost (£), PMS vs. SC	Incremental QALY, PMS vs. SC	ICER (£/QALY)
Base case			- 10433	15.2	686.9*
Costs (£)					
Cost of moderate FM/CWP, £907.2	£854.7	Lower and higher unit costs using NHS reference costs (184)	-10355.4	15.2	681.8*
	£939.2		-10480.29	15.2	690*
Cost of severe FM/CWP, £1227	£1174.6	Lower and higher unit costs using NHS reference costs (184)	-9668.2	15.2	636.6*
	£1259.1		10901.5	15.2	717.8*
Cost of PMS for mild FM/CWP, £181	£406	Assuming additional follow-up visit (+£225)	-10414.2	15.2	685.7*
Cost of PMS for moderate FM/CWP, £201	£426	Assuming additional follow-up visit (+£225)	-10343.4	15.2	681*
Cost of PMS for severe FM/CWP, £406	£631	Assuming additional follow-up visit (+£225)	-10374.7	15.2	683.1*
Utilities					
Utility of mild FM/CWP,0.65	0.76	Schaefer et al., (187)	-10433	18.3	569.7*
Utility of moderate FM/CWP,0.44	0.57		-10433	15	695.7*
Utility of severe FM/CWP,0.18	0.20		-10433	14.9	700.4*
Other parameters					
Discount rate,3.5%	0%	Arbitrary	-10834.6	27.3	379.2*
	6%		-9470.3	10.9	872.2*
**PMS is dominant*					

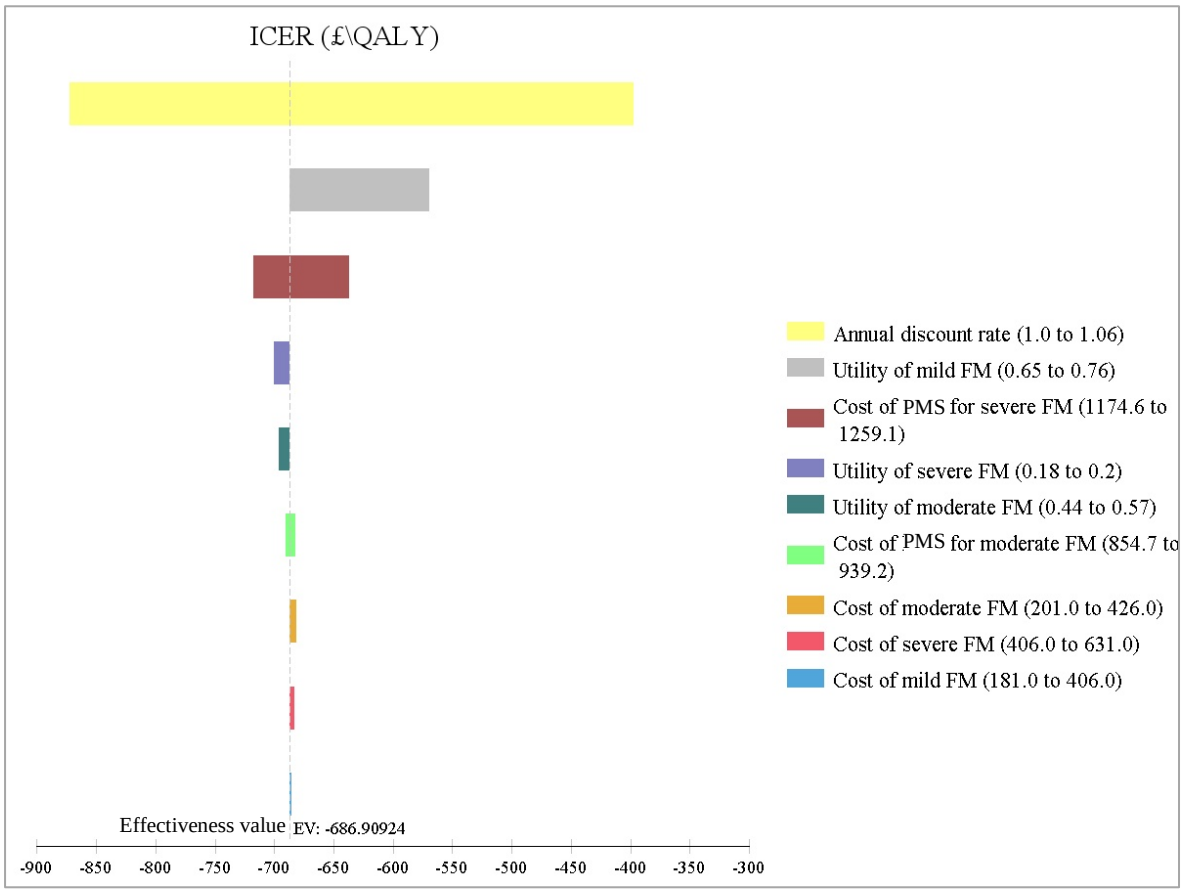


Figure 13. Tornado diagram demonstrating one-way sensitivity analysis of each variable in the model

5.4.3 Scenario analysis

The ICERs and cost-effectiveness acceptability curve (CEAC) generated for scenario analysis are shown in **Table 32**. In the analysis of different levels of FM/CWP severity entered in the model, PMS was slightly more cost-saving and generated more benefit than SC when applied to moderate or mild FM\CWP patients. When stratifying the severe patients to receive both pathways, PMS was the favoured strategy, with slightly lower QALYs and cost-saving than the base case (14.5 QALY and -£9525.9 vs. 15.2 QALY and -£10433). Regarding the probability of cost-effectiveness at a WTP threshold of £20000/QALY, the scenario analysis showed approximately similar figures, in which the probability that PMS is cost-effective exceeded 96.6% with 83%, 13.4%, 3% and 0.6% of ICERS located in the SE, NE, SW and NW quadrant, respectively.

Table 32. Mean and incremental cost, and QALYs, ICERs, percentage of ICERs in each quadrant of the cost-effectiveness plane, and probability of cost-effectiveness at WTP of £20000 for deterministic, PSA, and scenario analysis

Strategy	Cost (£)	Incremental cost (£), PMS vs. SC	Mean QALY	Incremental QALY, PMS vs. SC	Mean ICER (£/QALY)	% ICERs in each quadrant				Probability of CE at WTP of 20000
						SE	NE	SW	NW	
Base case (lifetime time horizon, 60 years)										
PMS	36209.8	-10433	34.8	15.2	686.9*	87	9.3	3.2	0.5	97
SC	46642.8		19.6							
Severe pain at baseline										
PMS	35081.7	-9525.9	34.08	14.5	657.6*	83	13.4	3	0.6	96.6
SC	44607.6		19.6							
Moderate pain at baseline										
PMS	34446.1	-11094.4	35.5	15.83	700.7*	87.8	8.8	3	0.4	97.4
SC	45540.5		19.6							
Mild pain at baseline										
PMS	33698.1	-10999.7	35.7	14.7	748.6*	86.2	9.2	3.8	0.8	96.4
SC	44697.9		21							
Time horizon of 5 years (20 cycles)										
PMS	10774.8	-4790.4	9.3	2.7	1802.6*	86.4	1	12.4	0.2	89.2
SC	15565.3		6.6							
Time horizon of 20 years (40 cycles)										
PMS	18136.7	-8496.2	17.5	5.9	1448.4*	89.6	1.2	8.8	0.4	92.6
SC	26632.9		11.6							
Time horizon of 40 years (160 cycles)										
PMS	34143.4	-11141.5	34.6	14.4	777.2*	85.4	8.8	4.8	0.8	94.8
SC	45284.8		20.2							

**PMS is dominant strategy. CE cost-effectiveness*

Table 32 (continued)

Strategy	Cost (£)	Incremental cost (£), PMS vs. SC	Mean QALY	Incremental QALY, PMS vs. SC	Mean ICER (£/QALY)	% ICERs in each quadrant				Probability of CE at WTP of 20000
						SE	NE	SW	NW	
Optimistic assumption: Attrition of effect= 0%										
PMS	34469.7	-8199.5	34.9	15.1	747.7*	86.2	9.4	3	1.2	96
SC	45767.7		19.8							
Pessimistic assumption: Attrition until all patients exited the model										
PMS	36333.4	-9049.4	31.3	12.1	680.4*	82	12.8	3.8	1.4	95.2
SC	44532.8		19.2							
Include suicide risk in moderate FM/CWP (SMRs=3, arbitrary)										
PMS	31303.7	-9799.6	32.1	13.9	703*	90.8	5.8	3.2	0.2	96.8
SC	41103.3		18.2							
Age-adjusted all-cause mortality rates without suicide risk										
PMS	37100.58	-23295.4	37.2	11.1	2102.7*	85.6	0.9	13.3	11.5	88.3
SC	60396.01		26.2							
Transition probabilities of two months data to derive the three months transition probabilities										
PMS	28649.6	-17968.7	39.5	21.6	833.7*	91	4.8	4.2	0	96.2
SC	46618.3		17.9							

**PMS is dominant strategy. CE cost-effectiveness*

The model was tested with a time horizon of five, twenty, and forty years against the base case lifetime time horizon (sixty years) (**Table 32**). The reason behind testing a shorter time horizon against the lifetime horizon in the scenario analysis is to investigate the cost-effectiveness of PMS against SC in different time-scales, which was considered important information if the future decision makers are interested in the benefits and costs of the intervention over a shorter period. PMS was estimated to be less costly, and resulted in improved QALYs over each of the modelled time horizons. The total generated QALYs with PMS are greater than with SC management, at reduced overall costs, for each of the time horizons modelled with an incremental gain increasing with the increase of the time horizon (2.7, 5.9, 14.4, and 15.2 QALYs and -£4790.4, -£8496.2, -£11141.5, and -£10433 from PMS in five-, twenty-, forty-year, and lifetime time horizons, respectively). This was because that the intervention reduced the suicidal effect by reducing the impact of FM of patients with years. Limiting the time horizon to a short period will not allow the full effect of the PMS intervention over time to be represented. There were 89.2%, 92.6%, and 94.8% probabilities that PMS dominated SC in the five-, 20- and 40-year time horizons, compared with 97% in the lifetime time horizon.

Regarding the attrition of effect, an optimistic scenario with absence of attrition for PMS effectiveness was slightly more cost-saving and generated more benefit than SC when compared with the base case (-£8199.5 vs. -£10433 and 15.1 vs. 15.2 QALYs for optimistic scenario vs. base case). CEAC analysis suggested 96% probabilities that PMS was cost-effective at the UK willingness-to-pay threshold of £20 000/QALY. In contrast, the analysis of a pessimistic assumption that applied attrition of PMS effect

until all patients exited the model showed that PMS was the favoured strategy over SC, with lower cost-saving and less generated QALYs compared with the base case analysis (-£9049.4 vs. -£10433 and 12.8 vs. 15.2 QALYs for the pessimistic scenario vs. base case). There was 95.2% probability that PMS dominated the SC in this scenario (with 82%, 12.8%, 3.8% and 1.4% of ICERS located in the SE, NE, SW and NW quadrant, respectively) compared with 97% in the lifetime time horizon.

When incorporating suicidal risk into moderate FM/CWP (SMR=3, arbitrary) as well as severe cases (SMR=6.5, based on Dreyer et al.(23)), the results suggest that PMS was the favoured strategy with 96.8% probability of cost-effectiveness at £20000/QALY, but with lower cost saving and less benefit than the base case analysis (-£9799.6 vs. -£10433.6 and 13.9 vs. 15.2 QALYs for suicidal risk in moderate and severe FM/CWP vs. base case). When the model was analysed without incorporating suicide risk, the result suggested that PMS was the preferred strategy, with 88% probability of cost-effectiveness at the UK willingness to pay threshold. The model generated fewer QALYs (11.1) but saved greater cost (-£23295.4) when compared with the base case analysis.

The final scenario tested the transition probabilities when derived from two-month data against the base case (transition probabilities derived from twelve-month data) from Luciano et al. (128). PMS was the dominant strategy over SC, with greater cost saving (-£17968.7) and generating more benefit (21.6 QALYs) compared with the base case analysis (-£10433 and 15.2 QALYs). CEAC analysis suggested 96.2% probability that

PMS was cost-effective at the UK willingness-to-pay threshold of £20 000/QALY, compared with a 97% probability for the lifetime time horizon.

5.5 Discussion

5.5.1 Principal findings

The economic evaluation presented in this chapter showed that the implementation of PMS intervention was associated with an increase in QALYs produced and was cost-saving to the NHS. With a 15.2 QALYs gain and -£10433 cost saving, the deterministic mean, ICER, was £686.9 per QALY gained for PMS versus SC. The probabilistic mean, ICER, was £723.4 per QALY gained for PMS versus SC (2.5% percentile -5053.1; 97.5% percentile 2340.92) with 87% of ICERs distributed in the SE quadrant of the cost-effectiveness plane, meaning that PMS is the dominant intervention. At a ceiling willingness to pay of £20000, the PMS intervention reached 97% probability of being cost-effective. The probability of PMS being cost-effective increased beyond 97% with other WTP thresholds in the CEAC. The incremental net monetary benefit statistic generated suggested a mean of £314199.2 net benefit at WTP threshold of £20000. The mean cost per QALY generated suggested that PMS increased health gain at a cost per QALY well below most accepted thresholds for implementation. Stratification of different FM/CWP severity levels to enter them in the model resulted in PMS being the favoured strategy for all severity levels, with a probability of being cost-effective which exceeded 96% at WTP threshold of £20000/QALY.

5.5.2 Strengths and weaknesses

Estimates of the cost-effectiveness of PMS compared with SC for the management of people with FM/CWP were obtained from a decision analysis model. This method has

many strong points. Firstly, based on the results of the systematic review presented in Chapter Three, to the researcher's knowledge, this economic evaluation is the first decision analysis model performed to evaluate the cost-effectiveness of PMS in FM/CWP. All the included studies in the systematic review were economic evaluations beside RCTs which provided data on cost-effectiveness limited to the time frame of the clinical trial (maximum time-frame was two years). Given the lack of longer-term evidence, using a decision analysis model allows for projection of QALYs, cost, and cost-effectiveness beyond the time point of the previously published clinical trials.

A second strength of this study is that the results of this economic analysis have been based on realistic assumptions of PMSs' effectiveness, by introducing the attrition of PMS effect for two years; therefore, the ICER estimates represent a conservative scenario, in which the QALYs and cost benefits of replacing SC with PMS are likely to be underestimated. Optimistic and pessimistic assumptions around attrition of effect were tested in many of the sensitivity analysis and the results were shown to be robust. In addition, more discounting and no further discounting were assessed in the OSA; therefore the base-case scenario was considered as a realistic assumption.

Thirdly, for the effectiveness of PMS in the base case analysis, data was derived from twelve-month data rather than two-month data, which is likely to overestimate the effect of PMS in the long term. This was considered as a realistic estimate of PMS. Varying the effectiveness to two-month data in the scenario analysis confirmed the assumption and resulted in a greater cost-saving and generated QALYs of PMS over SC when compared with the base case analysis.

Fourthly, the model analysis results presented in this chapter are based on cost-utility analysis, which enables the decision makers to make comparisons with other services. Further, the face validity of the de novo decision analytic model, including all inputs used to populate the model and the computerised model, was guarded throughout the development process by continuous consultation with pain experts, and health economics experts.

Conducting an economic evaluation using a decision analytic model requires attention to be paid to synthesising the evidence. Obtaining inputs for the decision analytic model was the key challenge. The key limitation of this analysis is the lack of long-term RCT data that quantify the actual clinical and economic effect of PMS in the UK. In addition, the sample size of the feasibility work performed in Chapter Four was very small (n=10), meaning the ability to apply data from it to the model was very limited. Instead of deriving data from expert opinion, which may be subject to bias, many communications with authors of published studies were undertaken to obtain patient level data, in order to parameterise inputs of effectiveness for the model. Obtaining such data by this method is challenging and not always feasible, as authors are usually reluctant to share patient level data or ethical approval by authors might be required to share the data.

For the economic data, the required data were obtained from other countries, which may not reflect the population and healthcare practice in the present study; therefore, validation with pain experts in the UK has been performed to reflect our patients and

setting. Future research is needed to quantify the actual clinical and economic effects of PMS in Nottingham, and to provide better data to populate the model.

Unlike the trial-based economic evaluations that are "piggy backed" on to clinical trials for the clinical and economic data, model-based economic evaluation synthesises all available secondary data sources, such as RCTs, observational trials, and expert opinion. Moreover, model-based economic evaluation allows for extrapolation of clinical and economic data for the lifetime horizon. Thus, it enables the projection of QALYs, cost, and cost-effectiveness beyond the time point of the previously published clinical trials. However, different data sources and extrapolation of data may raise the uncertainty in the model. Therefore, sensitivity analysis is a key component in decision analytic models. In this thesis, variations in model inputs were modelled in multiple, one-way and scenario analysis. In addition, probabilistic sensitivity analysis, which explores the joint impact of uncertainty across all parameters simultaneously, was also conducted.

5.5.3 Findings in relation to previous work

As mentioned above, this is the first decision analytic model used to evaluate the lifetime benefits and costs of PMS for people with FM/CWP. The systematic review described in Chapter Three found inconclusive evidence about the cost-effectiveness of PMS in FM/CWP, due to the methodological quality of the RCTs and the economic evaluations.

5.6 Conclusion

This chapter has suggested that the PMS pathway for the management of FM/CWP leads to a significant increase in health gain over the SC at a cost per QALY below most accepted thresholds for technology implementation. The conclusion was robust to the majority of sensitivity analysis undertaken, including the pessimistic scenario. If the hypothetical results found in the current chapter can be shown in practice, this would support the wider implementation of PMSs to manage people with FM/CWP in the UK and other healthcare systems.

Chapter 6: Statistical mapping of utility scores (EQ-5D-3L) from the revised fibromyalgia impact questionnaire (FIQR)

6.1 Introduction

As reported previously in the literature review, data on QALYs are not always collected as part of studies establishing clinical effectiveness of health technologies, but usually there are some sort of disease-specific health status measures used that are not designed to generate QALYs. Lack of availability of such data can be a problem for economic evaluations of those technologies. Therefore, statistical mapping can estimate health state utilities for HTAs from different measures of health. However, no mapping studies have been performed to map fibromyalgia-specific measures such as the FIQR to the most widely-used health related quality of life measure, the EQ-5D-3L (84).This chapter summarises NICE recommendations for the use of mapping methods to estimate health state utility values, and describe different estimation models and specifications that have been recommended in previous mapping studies. In addition, the direct relationship between the FIQR and EQ-5D-3L is examined using statistical mapping techniques. Comparative results are shown to choose the best performing model from various regression models.

6.2 Recommendations for the use of mapping methods

Due to the increased use of mapping techniques and the variability of available methods when considering mapping to estimate health state utilities for HTA, NICE has issued two technical advice reports to analysts on the methods for mapping (196, 197).

The NICE Methods Guide states that the EQ-5D-3L is the preferred target preference-based measure for mapping (196). This preference for EQ-5D is based on the need for

consistency across NICE appraisals. Moreover, the guide recommends that mapping should be performed on "empirical data" from trials rather than "expert opinion" (196). The guide outlines the three stages to perform mapping for researchers: firstly, identification of a dataset that contains the source and target measure; secondly, selection of appropriate regression methods to predict the target measure, either on the index score level or dimension score level; thirdly, the application of the regression method to the trial dataset to estimate the target measure. A final validation stage should be performed by the application of the regression results to another dataset to check the accuracy of the mapping equation. The technical aspects of mapping, including econometric methods, model specification and performance are summarised below.

6.2.1 Alternative regression models for mapping

A number of alternative econometric methods for mapping outlined by the NICE DSU technical support document can be used (83). These methods are: linear ordinary least squares (OLS), Tobit, censored least absolute deviation (CLAD), the two-part model (TPM), the generalised linear model (GLM), the latent class mixture model, the censored mixture model, and the multinomial logit model (MNL). There is no agreement on the best econometric method to use in mapping (198). The selection of the appropriate model is dependent whether the aim is to map the data onto the EQ-5D-3L index score (direct mapping) or the EQ-5D-3L dimension/domain score (response mapping). The assumptions of three of these regression models, along with the rationale for their choice are now discussed.

Ordinary least squares (OLS) model

OLS is the simplest and most common regression method for estimating the mean of the dependent variable. This model is able to predict the index score of the EQ-5D-3L (direct mapping). In the literature, OLS is the econometric method that has been most frequently used by mapping studies (86, 199). The main aim of this model is to minimise the sum of the squared residuals i.e. the difference between the observed value of EQ-5D-3L and the value predicted by the regression.

$$\boldsymbol{y_i = \alpha + \beta x_i + \varepsilon_i}$$

The formula above expresses observations on *y* (EQ-5D-3L) as a linear function of observations of $\boldsymbol{x}$ (FIQR) with slope β (beta), y-intercept α (alpha), and the error term ε (epsilon). In the OLS model, best estimations of EQ-5D-3L are predicted by minimising the sum of squared residuals, which is $\boldsymbol{\varepsilon}$ in the equation. Many underlying assumptions, including linearity, normality of the residual distribution and homoscedasticity, should be tested. Although these assumptions have been violated in many published mapping studies (200-202), it has been found that OLS gives the best overall performance compared with alternative econometric techniques (200-202). Details of these assumptions are found in **Appendix 17**.

The EQ-5D-3L index score usually exhibits a ceiling effect (83), i.e. a significant proportion of people report full health (EQ-5D-3L index=1), moderate health, or more severe health problems, resulting in a bimodal or multimodal distribution of EQ-5D-3L index; one peak around full health, one peak for moderate health, and a further peak

for more severe health problems. The OLS technique has been criticised for ignoring the ceiling effect, by not predicting the EQ-5D distribution for high and low values accurately, which may affect the robustness of the OLS estimator (83). Furthermore, the OLS model is not restricted to the bounded nature of the EQ-5D-3L index range e.g. -0.594 to 1 for the UK tariff values and -0.051 to 1 for Spanish tariff values (203), which may impact the accuracy of the predicted values and therefore lead to predicting values outside the range. However, despite these limitations, a review of 90 mapping studies found that 80% of the studies used the OLS (84). Moreover, a study found that OLS is the best method in reducing the errors of estimation, compared with other econometrics techniques (86, 204). Several alternative econometric methods have been proposed to overcome the limitations of OLS models, one of which is now described.

Censored least absolute deviation (CLAD) model

The censored least absolute deviation (CLAD) model is a median model which aims to minimise the sum of the absolute residuals from the regression line. Like OLS, the CLAD model is a direct mapping method which is able to predict the index score of the EQ-5D-3L. This model is preferable to OLS in the presence of ceiling effects and heteroscedasticity, i.e. the variance of the errors is not constant (86). This approach is based on an assumption that the median is more robust to ceiling effects and heteroscedasticity than the mean, as in OLS. The CLAD model with censoring at upper value of 1 is defined as follows (205):

$$\boldsymbol{y_i^* = \alpha + \beta x_i + \varepsilon_i}$$

$$y_i = \begin{cases} y_i^* \; if \; y_i^* < 1.0 \\ 1 \; if \; y_i^* \geq 1.0 \end{cases}$$

where y_i^* is a measure of the preference score the EQ-5D-3L, x_i is a vector of independent variables, β is a vector of the slope, α is the intercept, ε_i represents error terms or residuals that are independently and normally distributed, and y_i is the actual preference score as measured by the EQ-5D-3L.

Multinomial logit (MNL) model

The multinomial logit model is used an alternative approach to direct mapping by predicting the response level that patients select for each of the five EQ-5D-3L domains (206). Unlike direct mapping such as OLS and CLAD, this technique can give a richer insight into the relationship between EQ-5D-3L and FIQR by using FIQR responses to estimate the probable responses for each of the five domains in the EQ-5D-3L (207). A utility value can then be calculated for any country, without the need for separate models.

Multinomial logistic regression is the most commonly used method for response mapping (207), and is superior to other methods such as ordinal logistic regression (207), which relies on an assumption of proportional odds or parallel regressions that arrange the dependent variable categories in an ordered way. This results in different intercepts but the same coefficients for the explanatory variable i.e. differently ordered categorical variable have parallel slopes (207). Multinomial logistic regression is a multi-equation model, which generates equations where an outcome variable with *C* categories will generate *C*-1 equations for each domain. For example, for EQ-5D-3L

with 5 domains, each of which has three categories of levels, the total number of equations is 5 * (3-1) = 10 equations. Each equation will produce a coefficient i.e. log odds that compares that level with a reference group e.g. ‘extreme’ pain level in the EQ-5D-3L is compared with ‘no’ pain. Monte Carlo simulation is one of the methods used to produce the mapping function. This method was used previously by Gray et al. for response mapping between SF-12 and EQ-5D-3L (207).

6.2.2 Model specification

As previously mentioned, mapping can be performed either using direct mapping which predicts the index score or response mapping which predicts the dimension score of the dependent variable/target measure (EQ-5D-3L). There are other methods or “specifications” that can be utilised in the regression for mapping studies. These include the use of different levels of the independent variable/base measure. For example, in the FIQR, regression can be performed using: the total score, dimension score of the function, global impact and symptoms, or using the 21 items score. In addition, the regression can be applied using either continuous or discrete forms of any scores of the independent variable. Brazier and colleagues summarised the possible specifications that can be used in mapping studies (**Table 33**) (86). There are at least six specifications. Direct mapping using the OLS and CLAD to the index score of EQ-5D-3L can be performed in models 1 to 4 in **Table 33**, while response mapping, using the MNL model to the five dimensions of the EQ-5D-3L, can be performed in models 5 and 6.

Table 33. Recommended alternative specification of mapping function*

Specifications No.	Dependent variable/ target measure (EQ-5D)		Independent variable/source measure (FIQR)		Interactions	Other measures
	Main effect	**Discrete (D) or continuous (C)**	**Main effect**	**Discrete (D) or continuous (C)**		
1	Index score	C	Overall score	C	-	For any model: squared terms, other health measures, clinical measures, demographics
2	Index score	C	Dimension scores	C	Dimension	
3	Index score	C	Item score	C	Item levels	
4	Index score	C	Item score	D	Item levels	
5	Dimension score	C	Overall score/ Dimension scores/ Item score	C/D	Dimension/ Item levels	
6	Dimension score	D	Overall score/ Dimension scores/ Item score	C/D	Dimension/ Item levels	

*Adapted from (86)

Specification (1) is the simplest model, which regresses the total score of the target measure, index score of EQ-5D-3L, onto the total score of the base measure, the FIQR. This is the most limiting specification, as it assumes that the domains of the base measure are equally important. Therefore, more flexible and relaxed models, that reweight the information contained in the base measure, can be used by modelling the independent variable by either dimension/domain score (specification 2), item score (specification 3), or item responses (specification 4). The independent variable is treated as a continuous score in models1-3 and as a discrete dummy in model 4 (for example ‘all the time’ is one, otherwise zero, and so forth).

The use of item responses, specification 4, can result in a large number of independent variables (for example, the FIQR has over 200 possible responses) leading to collinearity problems. Being selective in items included by excluding the non-significant items, using step-wise regression analysis, prior to estimating a model with item responses is recommended (86).

The addition of more items to the model, such as squared terms for dimension or item scores and interaction terms, can relax the assumptions of specification 2-4. However, this can generate a large number of variables; so, as previously explained, limiting the variables to significant main effects can reduce the number of variables. Moreover, the addition of clinical measures or demographic data can improve the model. It would, however, limit the generalisability of the results and require the collection of identical clinical measures and patients’ demographics in other studies (199).

A more complex specification can be used by estimating the domain level of the target measure, the EQ-5D-3L (specification 5 and 6). This can estimate separate models for the five domains of the EQ-5D-3L by using any of the previous four specifications for the independent variable (overall score/ dimension scores/ item score); these models can create a dependent variable that can be treated as continuous (specification 5) or as discrete (specification 6).

6.2.3 Model performance

For any datasets analysed to estimate a dependent variable from a set of independent variables, methods for quantifying the accuracy of estimation or "goodness of fit" should be used. The NICE DSU technical support document recommends using the absolute difference (AD), mean absolute error (MAE), root mean squared error (RMSE), and R-squared (83). Each measure is described below.

- **Absolute difference (AD) -** The difference between the observed values and the predicted values is the AD, i.e. the vertical distance between an observed value and predicted value. This difference can also be referred to as "residuals" or "prediction errors". Ideally, the smaller the AD, the better the prediction. The equation for AD can be defined as:

$$AD = y - \bar{y}$$

  where y is the mean value of the observed values and $\bar{y}$ is the mean value of the predicted values.

- **Mean absolute error (MAE) –** the absolute mean value of the errors. As with the AD, the smaller the MAE, the better is the prediction. The equation for MAE can be defined as:

$$MAE = \frac{1}{n}\sum_{i=1}^{n} |y - \bar{y}|$$

- **Root mean squared error (RMSE) –** the standard deviation of $\bar{y}$ when $\bar{y} = a + bx$. RMSE can be calculated as the root of MAE (equation below). Since the RMSE is squared before the errors are averaged, this results in giving a relatively higher weight to larger errors, whereas MAE gives the absolute error.

$$RMSE = \sqrt{\frac{1}{n-2}\sum_{i=1}^{n} (y - \bar{y})^2}$$

- **R-squared (R^2) -** the proportion of the variation in the dependent variable that is explained by the independent variables (208). This measure has four elements: (1) predicting *y* without using *x*, (2) predicting y using information regarding *x*, (3) a summary measure of prediction errors for previous predictions, *E1* for errors by rule 1 and *E2* for errors by rule 2, and (4) the proportion of reduction in errors, as shown in this equation:

$$R^2 = \frac{E_1 - E_2}{E_1}$$

  The equation represents the concept of R^2 in reducing the errors by using the linear prediction equation instead of the sample mean. Ideally, a figure close to one is preferred for the R^2.

6.3 Summary of recommendations in the literature

This literature review has highlighted the importance of mapping studies for economic evaluation of interventions that lacked data on the preference based measures, specifically the EQ-5D-3L in the clinical trial. The economic evaluation of these

interventions is important to efficiently allocate resources. With more than 25% of economic evaluation submissions to NICE based on mapping, NICE has produced a guide for best methods in mapping. In FM/CWP, no mapping studies were found that map from the disease specific measure, the FIQR, to EQ-5D-3L. Lack of availability of such data can be a problem for economic evaluations of technologies in FM/CWP.

6.4 Objectives

The objectives of this chapter are to:

1- Map from FIQR as the source measure to the EQ-5D-3L utility score using direct mapping.
2- Map from FIQR as the source measure to the EQ-5D-3L domains using response mapping.
3- Identify the 'best' performing mapping function.
4- Describe the relationship between fibromyalgia impact (FIQR) and generic health status using the result of the direct and response mapping.

6.5 Methods

The methods of this part of the study follow the recommendations of NICE DSU (83) and the Mapping onto Preference-based measures reporting Standards (MAPS) (209, 210).

6.5.1 Measures

The target measure or dependent variable in this study was the EQ-5D-3L and the source measure or independent variable was the FIQR.

6.5.2 Estimation dataset

As the sample size of the current prospective cohort study reported in Chapter Four was inadequate to perform the mapping from FIQR to EQ-5D-3L, communication with authors of published studies who obtained data for both measures from adults with FM/CWP was undertaken, in order to obtain their anonymised datasets. Out of 12 communications with authors, one author agreed to provide his publication's datasets (211).

The data used in this study were obtained from a cross-sectional trial that aimed to subgroup a Spanish sample of fibromyalgia patients and to examine the difference between the groups in socio-demographic characteristics, functional status, using FIQR, and quality of life, using EQ-5D-3L (211). The sample consisted of 160 adults (≥18 years-old) with a confirmed diagnosis of FM according to the ACR 1990 criteria.

6.5.3 Analysis

6.5.3.1 Selection of modelling technique

Direct utility mapping models were estimated by regressing responses to individual FIQR questions directly onto the EQ-5D-3L index score using two functional forms: (1) Ordinary least squares (OLS) regression, (2) Censored least absolute deviations (CLAD), and response mapping by the multinomial logit model (MNL) performed to estimate the EQ-5D-3L domain score. The choice of these models was based on following considerations: for the OLS, it is the most widely used model and it was found in the literature that it gives best overall performance compared with other techniques (86). The second technique (CLAD) allows for the skewed distribution

(ceiling effect) of utility values and overcomes the violated assumptions of the OLS. The final technique was the MNL, which is the most common method to perform response mapping (207).

Before applying the OLS model on the dataset, five assumptions for OLS models were examined with the dependent variable, the EQ-5D-3L. These assumptions were linearity, normality, homoscedasticity i.e. the homogeneity of residuals variance, absence of multicollinearity, and random sample. Details of each assumption and specific test are presented in **Appendix 17**.

Following NICE DSU and MAPS recommendations (83, 209, 210), given the wide range of demographic variables included in the database such as age, sex, education level, and marital status, a backwards stepwise regression was used to identify the potential covariates for the regression and eliminate unnecessary or non-significant variables ($P \leq 0.05$ used as cut-off point). Age and educational status were the statistically significant variables and were included in the main regression for the mapping. All statistical analysis were performed using Stata version 14 (142).

6.5.3.2 Model specification

Table 34 shows ten model specifications that were used in the analysis. Assessment of total scores, domain scores and item responses for FIQR was performed. The simplest additive model (specification 1) regresses the EQ-5D-3L onto the global score of the starting measure, the FIQR total score. These assumptions can be relaxed by including domain scores and item responses as independent variables (specification 3-6 and 8-10). Total and domain scores were treated as continuous variables and item responses

were modelled as discrete dummy variables. To improve the performance of the model, backwards regression was performed, in which all possible covariates are included in the model and the least significant covariates removed. Age and education were identified as potential covariates and included in the model. For specification six and nine, it was necessary to collapse FIQR items into three levels (sores 0-3=mild, 4-7=moderate, 8-10= severe problem/impairment) to overcome the multicollinearity between FIQR items and EQ-5D-3L utility or domain score.

Table 34. Selected regression model specifications

Specification No.	Dependent variable	Independent variable
Direct mapping (OLS and CLAD models)		
1	EQ-5D-3L utility score	FIQR total score
2	EQ-5D-3L utility score	FIQR total score, age, education
3	EQ-5D-3L utility score	FIQR 3 domains (impairment, impact, symptoms), age, education
4	EQ-5D-3L utility score	FIQR 21 items (continuous), age, education
5	EQ-5D-3L utility score	FIQR 21 items (11 level discrete), age, education
6	EQ-5D-3L utility score	FIQR 21 items (three level discrete), age, education
Response mapping (MNL)		
7	EQ-5D-3L domain scores	FIQR total score
8	EQ-5D-3L domain scores	FIQR 3 domains (discrete)
9	EQ-5D-3L domain scores	FIQR 21 items (three level discrete)
10	EQ-5D-3L domain scores	FIQR 21 items (three level continuous)

6.5.3.3 Model performance

In order to produce a mapping equation that is able to accurately predict the dependent variable (EQ-5D-3L) from the independent variable (FIQR), evaluation of model performance is a key aspect for the accuracy of prediction. The performance of the models tested in this chapter was evaluated using the four estimates: AD, MAE, RMSE, and R^2 statistics. An estimate closer to zero is preferred for each of the AD, MAE, and RMSE statistics but a figure closer to one is preferred for R^2 statistics.

6.5.3.4 Model selection

When generating a mapping model, the factors that are important in selecting a model are accuracy of the mapped mean and the performance of the model, using AD, MAE, RSME, and R^2. The mapping and model fitting literature does not suggest a single criterion for use in selecting the best model when using multiple performance measures (83, 209, 210). Therefore, method used by Longworth and colleagues which ranks the performance statistics was used in this study (212).

This method is based on the premise that all performance statistics are ranked and scored using equal weighting, in order to ease the choice of best performing model among the ten models being evaluated by the four statistics. For example, having the lowest AD gets a rank of one (first), the next lowest AD score gets a score of two (second) and so on. The highest ranked R^2 gets a rank of one (first), the next highest score gets a score of two (second) and so on. Finally, all scores are summed and the lowest and highest total score indicates the best and worst performing model.

According to the NICE DSU document, some mapping studies have reported under-prediction for observed very mild utility scores and over-prediction for observed extremely severe utility, with better estimation for mild and moderate states (83). Therefore, NICE recommends that errors using MAR and RMSE should be reported across subsets of the EQ-5D-3L range to represent the effect on specific subgroups of patients (83). Examining the pattern of error across the scale of EQ-5D-3L is important to show whether the errors are affected by specific subgroups of patients with poor health and inform the application of the mapping algorithm (83). Therefore, for the best performing model, a sub-analysis was performed to examine the errors across four subsets of the EQ-5D-3L range ($0 \leq$ EQ-5D-3L< 0.25, $0.25 \leq$ EQ-5D-3L< 0.5, $0.5 \leq$ EQ-5D-3L< 0.75, $0.75 \leq$EQ-5D-3L≤ 1)

6.6 Results

6.6.1 Descriptive statistics

Table 35 presents the descriptive data of a sample of 160 patients who completed both EQ-5D-3L and FIQR questionnaires and were included in the analysis from Luciano et al. (211). The majority of respondents were females, with mean age of 57 years old, married, lived with someone, homemaker, and had primary education. The mean (SD) utility value on the EQ-5D-3L was 0.47 (0.22) on a scale of −0.654 to 1, and minimum and maximum scores of 0.01 and 0.84. The FIQR (range 0-100, higher scores indicate greater impact) showed a mean (SD) total score of 68.90 (18.87). **Figure 14** shows the usual multimodal distribution of the EQ-5D-3L utility index (as reported on page 175) and the normal distribution of FIQR total score.

Table 35. Socio-demographic and clinical characteristics

Characteristic	***N* = 160**
Mean (SD) age in years	57.3 (8.8)
Sex, female, n (%)	156 (97.5)
Education, n (%)	
Did not graduate from primary school	33 (20.6)
Primary school	86 (53.8)
Secondary school	35 (21.9)
University	6 (3.75)
Marital status, n (%)	
Single	5 (3.13)
Married/Living with a partner	118 (73.6)
Separated/divorced	20 (12.5)
Widowed	17 (10.6)
Living arrangement, n (%)	
Living alone	18 (11.2)
Living with someone (spouse/partner/relative)	142 (88.8)
Work status, n (%)	
Homemaker	40 (25)
Paid employment	25 (15.6)
Paid employment but on sick leave	7 (4.4)
Unemployed with allowance	25 (15.6)
Unemployed without allowance	14 (8.8)
Retired/pensioner	25 (15.6)
Others (e.g. student)	24 (15)
Mean years of diagnosis (SD)	9.45 (6.6)
Total FIQR (1-100)	
Mean (SD)	68.90 (18.87)
Median (IQR)	70.75 (26.17)
Minimum-maximum score	6-98
EQ-5D-3L utility value (−0.654 - 1)	
Mean (SD)	0.47 (0.22)
Median (IQR)	0.48 (0.42)
Minimum-maximum score	0.01-0.84

(a) FIQR total score (b) EQ-5D-3L utility

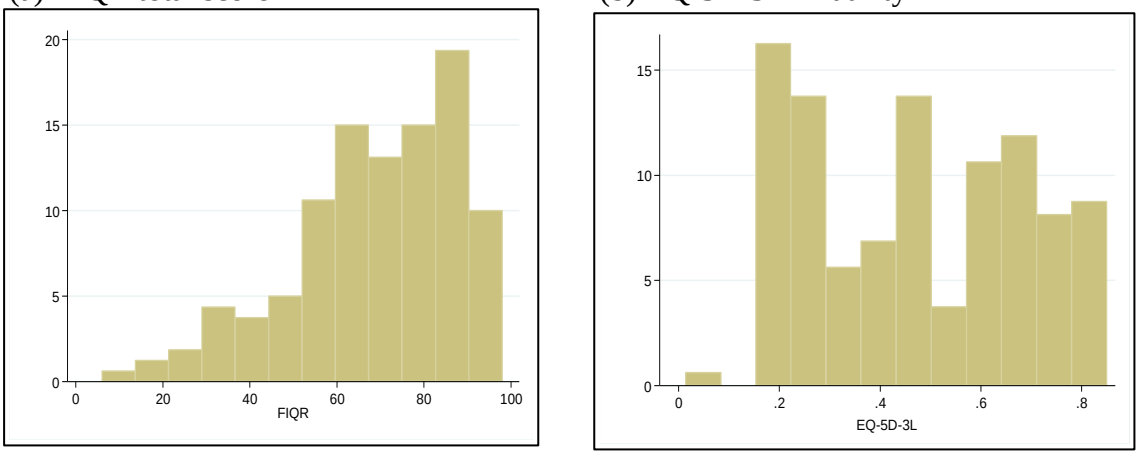


Figure 14. Distribution of (a) FIQR total score and (b) EQ-5D-3L utility index

6.6.2 Summary results of OLS assumptions:

Five basic assumptions were tested (as shown in **Appendix 17**); a summary of these results is as follows:

1- The normality assumptions of the residuals were checked and the results suggest that the residuals were not normally distributed.
2- The assumption of the homoscedasticity of the residuals was confirmed graphically and statistically.
3- The multicollinearity test using the Variance Inflation Factor (VIF) suggested that there was no collinearity between independent variables.
4- The linearity test suggested that there was a small degree of non-linearity between the EQ-5D-3L and the FIQR.
5- The assumption of a random sample is not of concern for this analysis, because the samples in Luciano et al. are assumed to be a random sample of FM/CWP patients due to the method of recruitment (211).

6.6.3 Models' prediction and overall performance

The results shown in this section represent mapping to EQ-5D-3L from FIQR using three types of models: OLS and CLAD for direct mapping, and MNL for response mapping. Choice of model was based on the 'Best' performance which is defined as: the lowest AD, lowest MAE, lowest RMSE, or the highest R^2 statistics. The 'Worst' model was defined as having the highest AD, MAE, or RMSE, or the lowest R^2 statistics.

Table 36 presents the observed EQ-5D-3L values, mapped EQ-5D-3L values, and performance statistics of the models, using the three econometric methods. From the table, it can be seen that all OLS models were able to predict the mean observed EQ-D-3L (0.4737) to up to four decimals, compared to CLAD and MNL models that were able to predict up to only one decimal. Over-prediction and under-prediction of the observed range was observed in all models. The OLS models were the most able to predict the observed maximum (0.8498) value by one decimal among other models.

Table 36. Results of regression model specifications

Model			EQ-5D-3L Observed values			EQ-5D-3L Predicted values			Model performance			
No.	**Specification**	**N**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**	**AD**	**MAE**	**RMSE**	**R^2**
Regression model: OLS												
1	1	160	0.4737	0.014	0.8498	0.4737	0.3085	0.8310	**0.0000**	0.1631	0.1873	0.2478
2	2	160	0.4737	0.014	0.8498	0.4737	0.2545	0.8373	**0.0000**	0.1561	0.1826	0.2854
3	3	160	0.4737	0.014	0.8498	0.4737	0.2620	0.8881	**0.0000**	0.1550	0.1808	0.2991
4	4	160	0.4737	0.014	0.8498	0.4737	0.2235	0.8939	**0.0000**	0.1416	0.1686	0.3904
5	5	160	Model not worked (multicollinearity). Scales of FIQR items converted from 11 to 3 (model 6)									
6	6	160	0.4737	0.014	0.8498	0.4737	0.1749	0.8794	***0.0000***	**0.1279**	***0.1576***	***0.4675***
Regression model: CLAD												
7	1	160	0.4737	0.014	0.8498	0.4862	0.2819	0.9281	**0.0000**	0.1608	0.1895	0.2478
8	2	160	0.4737	0.014	0.8498	0.4993	0.2180	0.8931	**0.0000**	0.1549	0.1871	0.2734
9	3	160	0.4737	0.014	0.8498	0.4842	0.1707	0.9898	**0.0000**	0.1525	0.1876	0.2744
10	4	160	0.4737	0.014	0.8498	0.4695	0.1461	1.1726	0.0043	0.1333	0.1828	0.3355
11	5	160	Model not worked (multicollinearity). Scales of FIQR items converted from 11 to 3 (model 6)									
12	6	160	0.4737	0.014	0.8498	0.4627	0.0462	0.9549	0.0109	***0.1168***	**0.1777**	**0.3898**
Regression model: MNL												
13	7	160	0.4737	0.014	0.8498	0.4171	-0.0490	0.905	0.0567	0.2580	0.3160	0.0474
14	7	160*100	0.4737	0.014	0.8498	0.4248	-0.3300	1.0000	0.0489	0.2496	3.115	0.0833
15	8	160	The model doesn't work as discrete, the results below are continuous									
16	8	160	0.4737	0.014	0.8498	0.4127	-0.1580	0.905	0.0610	0.2501	**0.3111**	0.0756
17	8	160*100	0.4737	0.014	0.8498	0.4252	-0.3300	1.0000	**0.0484**	**0.2445**	3.0587	**0.1005**
18	9	160	The model keeps iterating with discrete variables. Might be due to a lack of variability in responses to allow the model to establish a relationship between the dependent and independent variables for the model to converge 'stop iterating'.									
19	10	160										

AD absolute difference, MAE mean absolute error, RMSE root mean squared error.

Model 14 and 17 were iterated with 100 iterations.

NB: best performing model judged by lowest AD, MAE, RMSE or highest R^2 statistic.

***BOLD** = performed best within statistic within model; italics = performed best within statistic across models; underlined = best model across all model performance statistics.*

6.6.4 Model selection

Table 37 represent the ranking of all models based on their performance. Out of thirteen rankings, model 6 of the OLS (independent variables: FIQR items in three level discrete form, age, and education level) is the best performing model (total rank was first), with the lowest AD (0.0000) and RMSE (0.1576) and highest R^2 (0.4675). The lowest MAE score (0.1168) was produced by model 12 (CLAD, with a total rank of third), which was the best CLAD model overall, but with higher AD (0.0109), and RMSE (0.1777), and lower R^2 (0.3898) than model 6 (OLS model). The smallest AD was produced by all OLS models and three CLAD models (models 1- 9). All MNL models performed 'worst' overall across all statistics (total rank 10^{th} to 13^{th}). Multiple simulation of MNL models (model 14 and 17) improved their performance (total rank 11^{th} and 12^{th}); however, they still performed the worst overall.

Table 37. Primary model choice by overall ranked score of performance across regression models

Model			Model performance				Ranked score*				Total score	Total rank#
Regression type	No.	Spec.	AD	MAE	RMSE	R^2	AD	MAE	RMSE	R^2		
OLS	1	1	0.0000	0.1631	0.1873	0.2478	1	10	8	10	29	8
	2	2	0.0000	0.1561	0.1826	0.2854	1	8	5	6	20	6
	3	3	0.0000	0.155	0.1808	0.2991	1	7	4	5	17	5
	4	4	0.0000	0.1416	0.1686	0.3904	1	4	2	2	9	2
	6	6	0.0000	0.1279	0.1576	0.4675	1	2	1	1	5	**1**
CLAD	7	1	0.0000	0.1608	0.1895	0.2478	1	9	10	9	29	8
	8	2	0.0000	0.1549	0.1871	0.2734	1	6	7	8	22	7
	9	3	0.0000	0.1525	0.1876	0.2744	1	5	9	7	22	7
	10	4	0.0043	0.1333	0.1828	0.3355	2	3	6	4	15	4
	12	6	0.0109	0.1168	0.1777	0.3898	3	1	3	3	10	3
MNL	13	7	0.0567	0.258	0.316	0.0474	6	14	12	14	46	13
	14	7	0.0489	0.2496	3.115	0.0833	5	12	14	12	43	11
	16	8	0.061	0.2501	0.3111	0.0756	7	13	11	13	44	12
	17	8	0.0484	0.2445	3.0587	0.1005	4	11	13	11	39	10

** low ranking provided for the model with smallest errors (error near to zero for AD, MAE, RMSE, and near to 1 for R^2)*
 # low rank was given for models with smallest total score
AD absolute difference, MAE mean absolute error, RMSE root mean squared error.

6.6.5 The performance of best model by categorised EQ-5D-3L score

Table 38 shows two particular errors or performance statistics, MAE and RMSE, of the best model (OLS model 6: FIQR 21 items in three level discrete, age, and education level as independent variables) when mapped to four subsets of EQ-5D-3L range. Few patients within the sample reported very low or very high utility scores; fourteen patients (8.8%) had an EQ-5D-3L tariff score in the top quartile of the score range (EQ-5D-3L score 0.75 to ≤ 1), and 37 patients (23.1%) had EQ-5D-3L tariff scores in the bottom quartile of the score range (EQ-5D-3L score of 0.25 or less).

Across the scale of EQ-5D-3L, the degree of error was not evenly distributed. The level of performance errors in low health states (EQ-5D-3L= 0 – 0.249) and high health states (EQ-5D-3L= 0.75- 1) were equal to zero in MAE and RMSE (preferred). A higher level of error was found at score ranges near to the mean EQ-5D-3L value (EQ-5D-3L score= 0.25 - 0.499; MAE=0.0264, RMSE= 0.0379) than the full index errors (MAE=0.1279, RMSE= 0.1576). This result indicates that there is a low tendency for the model to over or under predict values for score ranges of extremely severe and mild utilities.

Table 38. Mean Absolute Error and Root Mean Squared Error of best model (model 6), by EQ-5D Index Range

EQ-5D score	N	%	MAE	RMSE
0 – 0.249	37	23.1	0	0
0.25 - 0.499	54	33.8	0.0264	0.0379
0.5 - 0.749	55	34.4	0.0201	0.0262
0.75- 1	14	8.8	0	0
Full index	160	100	0.1279	0.1576

6.6.6 Model coefficients: Direct mapping using OLS and CLAD to EQ-5D-3L tariff score

Coefficients of all independent variables, including age and educational level, and the intercept of the regression line, with the significance level, for all tested models are presented in **Table 39**

6.6.6.1 Association between FIQR total impact and EQ-5D-3L

The models that used FIQR total score as the independent variable are Models 1 and 2 in the OLS Model and 7 and 8 in the CLAD model. Significant association ($p< 0.01$) was found between FIQR total score and EQ-5D-3L tariff score, with coefficients ranging from 0.006-0.007 across all four models. The relationship can be translated in Model 1 as meaning that, for every one-unit increase in FIQR score, the EQ-5D-3L tariff score will statistically significantly decrease by 0.006. Note that age and educational level are accounted for in Models 2 and 8.

6.6.6.2 *Association* between FIQR domain impact and EQ-5D-3L

Model 3 (OLS model) and Model 9 (CLAD model) used the domain score of FIQR as the independent variable. Of the three domains, Impairment and Symptoms were statistically significantly associated with the EQ-5D-3L tariff score ($p<0.01$ in model 3, $p<0.05$ in model 9) with estimated coefficients ranging between: -0.009 to -0.01 for impairment and -0.007 to -0.01 for symptoms. Model 3 was the better performing model of the two and estimated that for, any one-unit increase in FIQR domain score, the tariff score will decrease by: 0.009 (impairment); 0.001 (impact); and 0.007 (symptoms). Note that age and educational level are accounted for in this model.

6.6.6.3 Association between FIQR items' impact (continuous variable) and EQ-5D-3L

In models 4 (OLS) and 10 (CLAD), FIQR items were modelled as continuous independent variables. Significant relationships with EQ-5D-3L were found in: level of depression (both models, coefficient range -0.009 to -0.013), anxiety (model 4, coefficient= -0.014), balance problems (model 10, coefficient= -0.019), and ability to walk continuously for 20 minutes (model 10, coefficient= -0.011). The remaining FIQR items were not statistically significant associated with EQ-5D-3L domain score.

From **Table 39**, model 4 (OLS) was better in predicting the tariff score than model 10 (CLAD), by performance statistics, and estimated that for any one-unit change in FIQR items score (as a continuous variable), tariff score will change by: - 0.003 (brush or comb hair); -0.006 (ability to walk continuously for 20 minutes); -0.003 (prepare a home-made meal); 0.002 (vacuum, scrub, or sweep floors).

Table 39. Independent variable coefficients by regression model with EQ-5D-3L as dependent variable

No.	Spec.	Total score	Impairment domain or items score [a]																	
			Brush or comb hair		Walk continuously for 20 minutes		Prepare a homemade meal		Vacuum, scrub or sweep floors		Lift and carry a bag full of groceries		Climb one flight of stairs		Change bed sheets		Sit in a chair for 45 minutes		Go shopping for groceries	
			Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.
Regression model: OLS																				
1	1	-0.006[3]	-		-		-		-		-		-		-		-		-	
2	2	-0.006[3]	-		-		-		-		-		-		-		-		-	
3	3	-	-0.009[3]																	
4	4	-	-0.003		-0.006		-0.003		0.002		0.004		-0.001		-0.001		-0.008		-0.011	
5	5																			
6	**6**	**-**	**-0.007**	**-0.003**	**-0.043**	**-0.069**	**0.059**	**0.001**	**-0.044**	**-0.007**	**0.119**	**0.183[1]**	**-0.116**	**-0.112**	**0.045**	**-0.005**	**-0.038**	**-0.056**	**-0.120[1]**	**-0.164[2]**
Regression model: CLAD																				
7	1	-0.007[3]	-		-		-		-		-		-		-		-		-	
8	2	-0.007[3]	-		-		-		-		-		-		-		-		-	
9	3		-0.010[2]																	
10	4		-0.010		-0.011[1]		0.005		0.013		0.016		0.004		-0.007		-0.008		-0.022[1]	
11	5																			
12	6	-	-0.041	-0.021	-0.008	-0.070	0.096	0.025	0.062	0.043	0.123	0.267	-0.199	-0.220	0.085	0.050	-0.047	-0.078	-0.182	-0.222[2]

[1] p<0.1., [2] p<0. 05, [3] p<0.01

Mod. Moderate level score (5-6), Sev. Severe level score (7-10). The base case comparison group is 'mild' (score 0-4). **BOLD =** coefficients of best performing model

Table 39 (continued)

No.	Spec.	Impact total, domain or items score				Symptoms total, domain or items score													
		Fibromyalgia prevented the accomplishment of goals for the week		Completely overwhelmed by fibromyalgia symptoms		Pain level		Energy level		Stiffness level		Sleep quality		Depression level		Memory problems level		Anxiety level	
		Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.	Mod.	Sev.
Regression model: OLS																			
1	1	-		-		-		-		-		-		-		-		-	
2	2	-		-		-		-		-		-		-		-		-	
3	3	-0.001				-0.007[3]													
4	4	-0.006		0.005		-0.001		-0.001		-0.001		-0.003		-0.009[1]		0.009		-0.014[2]	
5	5																		
6	**6**	**-0.079[1]**	**-0.050**	**-0.079[1]**	**-0.050**	**0.006**	**-0.011**	**0.062**	**-0.007**	**-0.019**	**0.016**	**-0.075**	**-0.073**	**-0.031**	**-0.09[1]**	**0.127[2]**	**0.113[2]**	**-0.051**	**-0.076**
Regression model: CLAD																			
7	1	-		-		-		-		-		-		-		-		-	
8	2	-		-		-		-		-		-		-		-		-	
9	3	0.001				-0.0102													
10	4	-0.012		0.005		0.000		0.008		0.003		-0.003		-0.0132		0.015		-0.012	
11	5																		
12	6	-0.137	-0.093	0.069	0.059	0.157	0.183	0.108	0.080	0.011	0.050	-0.187	-0.241[1]	-0.044	-0.134	0.202[2]	0.162	0.015	-0.057

[1] p<0.1., [2] p<0. 05, [3] p<0.01

Mod. Moderate level score (5-6), Sev. Severe level score (7-10). The base case comparison group is 'mild' (score 0-4). **BOLD =** coefficients of best performing model.

Table 39 (continued)

No.	Spec.	Symptoms total, domain or items score						Age	Primary school [d]	Secondary school [d]	University [d]	Intercept
		Level of tenderness to touch		Level of balance problems		Level of sensitivity to loud noises, bright lights, odors and cold						
		Mod.	Sev.	Mod.	Sev.	Mod.	Sev.					
Regression model: OLS												
1	1	-		-		-		-	-	-	-	0.865[3]
2	2	-		-		-		0.003	0.048	0.116[2]	0.028	0.638[3]
3	3							0.003	0.037	0.104[2]	0.01	0.711[3]
4	4	0.001		-0.008		-0.001		0.002	0.03	0.099[1]	-0.009	0.658[3]
5	5											
6	**6**	**0.032**	**0.042**	**0.025**	**-0.027**	**-0.052**	**-0.059**	**0.002**	**0.030**	**0.088[1]**	**-0.045**	**0.504[3]**
Regression model: CLAD												
7	1	-		-		-		-		-		0.970[3]
8	2	-		-		-		0.005	0.088	0.155[2]	0.110	0.559[3]
9	3							0.005	0.124[1]	0.215[3]	0.075	0.617[2]
10	4	0.004		-0.019[2]		-0.006		0.003	0.079	0.137[1]	0.025	0.500[1]
11	5											
12	6	0.041	0.035	0.035	-0.045	-0.104	-0.136	0.000	0.034	0.084	-0.091	0.529

[1] p<0.1., [2] p<0. 05, [3] p<0.01

Mod. Moderate level score (5-6), Sev. Severe level score (7-10). The base case comparison group is 'mild' (score 0-4). **BOLD =** coefficients of best performing model.

Association between FIQR items' impact (discrete variable) and EQ-5D-3L

Model 5 (OLS), and Model 11 (CLAD), used the 21 FIQR items as discrete variables. These resulted in multicollinearity in the model by developing more than 231 dummies for the FIQR (21 items * 11 points scale). Therefore, the collapse of the eleven-point scale to three scales: (0-4) representing no or mild scores, (5-6) representing moderate scores, and (7-10) representing severe or extreme scores, was used.

The new collapsed FIQR items were tested in model 6 (OLS) and model 12 (CLAD). Moderate (model 6) and severe (model 6 and 12) difficulty in "Go shopping for groceries" and "memory problems", severely low "sleep quality" (model 12), severe (model 6) difficulty in "lifting or carrying bag full of groceries", severe level of "Depression", and moderate level of "Prevention from accomplishing goals of the week" were significantly associated with the EQ-5D-3L tariff score. The remaining items were not statistically significant ($p > 0.1$).

Model 6 was the best performing model across all models in this chapter. This model estimated that for any one unit change in FIQR item score (as a discrete variable), utility was statistically significant changed by: 0.183 (severe difficulty with lifting or carrying a bag full of groceries), -0.12 (moderate difficulty with going shopping for groceries), -0.164 (severe difficulty with going shopping for groceries), -0.079 (moderate level of prevention from accomplishing goals of the week), -0.089 (severe level of depression), 0.127 (moderate level of memory problems) and 0.113 (severe level of memory problems) (**Table 39**). Note that age and educational level were accounted for in this model.

6.6.6.4 Association between age, or education and EQ-5D-3L

For models 2 to 12, age was not significantly associated with the EQ-5D-3L tariff score. In the Educational level variable, secondary education was significantly associated with an increase in the tariff score in models 2 to 4 in OLS, and models 8 to 10 in CLAD. Primary education was only significantly associated with an increase in the tariff score in model 9 in CLAD. University education was not significantly associated with the tariff score in all models, 2 to 12. Across all models, estimated coefficients for age and education level ranged from: 0 to 0.005 for age, 0.03 to 0.124 for primary school, 0.84 to 0.215 for secondary school, and -0.009 to 0.11 for university level of education.

6.6.7 Model coefficients: response mapping to the EQ-5D-3L domain score

In the MNL models, model 17 was the best performing model (AD=0.0484, MAE= 0.2445, RMSE= 3.0587. R2= 0.1005) when compared with other MNL models **(Table 37).** This finding suggests that when using MNL models to map from FIQR to EQ-5D-3L, the best model is to map from the FIQR domains score as the independent variable with 100 iterations of the sample. Generally, however, this model is not superior or similar to OLS or CLAD models in performance statistics.

Response mapping using individual 21 FIQR items in a discrete form (model 18) was tested but convergence was not achieved. Further analysis for item responses in a continuous form (model 19) did not solve the non-convergence problem. This is maybe due to the lack of variability in responses to allow the model to establish a

relationship between the dependent (EQ-5D-3L) and independent (FIQR) variables for the model to converge.

Table 40 reports the MNL regression results for each of the EQ-5D-3L domains, using the total FIQR score or individual FIQR domains' responses as independent variables. The log odds presented in **Table 40** could be used in response mapping. The interpretation of log odds is not always straightforward. The log odds represent the likelihood that one outcome will occur by the effect of group *b* in relation to group *a* in one predictor. In which, group *a* is the base case of 'no' problems within each EQ-5D-3L domain and group b is any other item level ('some', and 'extreme') within each domain.

Table 40. Log odds from multinomial logistic regression using EQ-5D-3L domain scores and FIQR total and domain scores*

	EQ-5D-3L									
	Mobility		Self-care		Usual activities		Pain/discomfort		Anxiety/depression	
	Some	Extreme	Some	Extreme	Some	Extreme	Some	Extreme	Some	Extreme
FIQR total score										
Total score	0.03[2]	0.00	0.04[3]	0.86	0.06[3]	0.88	0.07[2]	0.10[3]	0.05[3]	0.10[3]
Intercept	-1.79[2]	0.00	-2.62[3]	-82.84	-3.68[3]	-84.26	-0.89	-3.15[2]	-3.12[3]	-6.87[3]
FIQR Domains										
Function	0.14[3]	0.00	0.109[2]	35.98	0.14[2]	34.33	0.00	0.06[2]	-0.01	0.00
Overall impact	-0.03	0.00	0.03	-3.75	0.04[1]	-3.51	0.02	-0.02[2]	0.03	0.09[1]
Symptoms	-0.01	0.00	0.02	6.38	0.02	6.00	0.17[1]	0.23	0.14[3]	0.20[3]
Intercept	-2.2[2]	0.00	-2.51[2]	-1266.06	-3.61[3]	-1204.32	-1.93	-5.39	-4.60[3]	-8.33[3]

**The base case comparison group is no problem for the EQ-5D-3L and no/mild impairment for the FIQR. The item levels for the EQ-5D-3L are some and extreme, and the item levels for the FIQR are moderate and severe impairment. For the item log odds, the model keeps iterating*

[1] p<0.05, [2] p<0. 01, [3] p<0.001

In the response mapping of FIQR total score, strong relationships were observed with mobility ('some' only, $p<0.01$), self-care ('some' only, $p<0.001$), usual activity ('some' only, $p<0.001$), pain/discomfort ($p<0.01$), and anxiety/depression ($p<0.001$). The results from **Table 40** suggest that higher levels of FIQR total score (high FM impact) were associated with increased odds of reporting 'some' or 'extreme' problems in EQ-5D-3L domains. To interpret this relationship when associating FIQR total score with 'some' problems in the pain/discomfort domain in the EQ-5D-3L, the result can be written as follows: one-unit increase in FIQR total score is significantly associated with a 0.074 increase in the log odds of having 'some' pain or discomfort versus 'no' pain or discomfort ($p<0.001$).

For FIQR-domain responses, statistically significant relations with EQ-5D-3L item responses were found (**Table 40**). One example of the relationship between the 'symptom' domain in FIQR and 'extreme' anxiety/depression domain in EQ-5D-3L can be translated as for every one-unit increase in FIQR-symptoms score, there is a 0.205 unit increase in the relative odds of having 'extreme' anxiety/depression compared with 'no' anxiety/depression.

The following section discuss the coefficients and significance level shown in **Table 40**. The sub-sections are categorised by the EQ-5D-3L domains in order to discuss the effect of total FIQR score and domain responses on EQ-5D-3L domains. Significant results and log odds are now presented and discussed.

6.6.7.1 Association between FIQR total score, FIQR domains and EQ-5D-3L mobility domain

For the FIQR total score, the results suggest that every one unit of deterioration (higher FIQR total score) was significantly ($p<0.01$) associated with a 0.03 increase in the log odds of having 'some' mobility problem in EQ-5D-3L, versus 'no' problem. A statistically non-significant relationship was found between total FM score and the odds of having 'extreme' mobility problem, versus 'no' problem. This result seems to suggest that having a higher FM impact will not change the log odds of having 'extreme' problems, versus 'no' mobility problems.

In the domain of FIQR, having 'some' mobility problems, but not 'extreme' problems, will significantly increase the odds by 0.14 ($p<0.001$) for every one unit increase in function domain score relative to 'no' problems in mobility. Symptoms and overall impact domains were not statistically significantly associated with the change of mobility log odds.

6.6.7.2 Association between FIQR total score, FIQR domains and EQ-5D-3L self-care domain

For the FIQR total score, the results suggest that for every one unit of deterioration in a person's FM impact (higher FM total score), this was significantly ($p<0.001$) associated with a 0.04 increase in the log odds of having 'some' self-care problem, versus 'no' problem. A statistically non-significant relationship was found between total FM score and the odds of having 'extreme' self-care problem, versus 'no' problem. This result seems to suggest that having higher FM impact will significantly

change the log odds of having ‘some’, but not ‘extreme’ problems, versus ‘no’ self-care problems.

The former result was consistently seen with the domain of FIQR, in which the relative log odds of having ‘some’ self-care problems, but not ‘extreme’ problems, will significantly increase the odds by 0.109 ($p<0.01$) for every one unit increase in function domain score relative to ‘no’ problems. Symptoms and overall impact domains were not statistically significantly associated with the change of self-care log odds.

6.6.7.3 Association between FIQR total score, FIQR domains and EQ-5D-3L usual activity domain

For the FIQR total score, the result suggests that for every one unit of deterioration in a person’s FM impact (higher FM total score), this was significantly ($p<0.001$) associated with a 0.06 increase in the log odds of having ‘some’ usual activity problems, versus ‘no’ problems. A statistically non-significant relationship was found between the total FM score and the odds of having ‘extreme’ usual-activity problems, versus ‘no’ problems. This result seems to suggest that having higher FM impact will significantly change the log odds of having ‘some’, but not ‘extreme’ problems, versus ‘no’ usual-activity problems.

The former result was consistently seen with the function and overall impact domains of FIQR, in which the relative log odds of having ‘some’ usual-activity problems, but not ‘extreme’ problems, relative to ‘no’ problems, will significantly increase the odds by 0.109 ($p<0.01$) for every one unit increase in function or overall impact domain

score. The symptoms domain was not statistically significantly associated with the change of usual-activity log odds.

6.6.7.4 Association between FIQR total score, FIQR domains and EQ-5D-3L pain/discomfort domain

For the FIQR total score, the result suggests that for every one unit of deterioration in a person's FM impact (higher FM total score), this was significantly ($p<0.01$) associated with increase in the log odds of having 'some' or 'extreme' usual-activity problem, versus 'no' problem. This result suggests that having lower FM impact will have significant effect in lowering the odds of all levels of pain to 'no' problems in pain/discomfort

Function and overall impact domains were significantly associated with 'extreme' problems of pain/discomfort ($p<0.01$). For the function domain, every one-unit increase will significantly increase the odds of having 'extreme' pain by 0.06 relative to 'no' problems. The symptoms domain was also significantly associated with developing pain but to 'some' pain level from 'no' pain, in which the odds increase by 0.166 ($p<0.05$).

6.6.7.5 *Association between FIQR total score, FIQR domains and EQ-5D-3L anxiety/depression domain*

The relation between the total FIQR score and anxiety/depression suggests that having a lower FM impact will have significant effect ($p<0.001$) in lowering the odds of all

levels of anxiety/depression (by 0.05 from ‘some’ and 0.10 from ‘extreme’) to ‘no’ problems in anxiety/depression.

In the FIQR domain level, symptoms have the same effect on total FIQR score, in which having lower symptoms scores will have significant effect ($p<0.001$) in lowering the odds of all levels of anxiety/depression (by 0.14 from ‘some’ and 0.20 from ‘extreme’) to ‘no’ problems in anxiety/depression. This result showed that the symptom domain is highly related or similar to the anxiety/depression domain of the EQ-5D-3L: even when comparing the odds of moving from ‘some’ or ‘extreme’ pain to ‘no’ pain, the odds are higher from the symptom domain than from total FIQR score. The effect of total score was diluted by the non-significant effect of the other items of the FIQR (function and overall impact).

6.6.8 Summary of key results and mapping algorithm

The analysis of the results in this chapter examined whether it was feasible to map from a fibromyalgia/chronic widespread pain-specific measure that measures the impact of FM/CWP (FIQR) to the NICE recommended preference based measure (EQ-5D-3L), using data from a sample of Spanish adults with FM/CWP.

The analysis here showed that the best mapping model, based on model performance, was model 6 in the OLS which models the EQ-5D-3L tariff score from FIQR items’ level (3-levels and discrete-form score), age, and educational level. This model was able to predict up to four decimals of the observed EQ-5D-3L and one decimal to the ranges. Other models were able to map the FIQR to the EQ-5D-3L; however, the performance of these models was not superior to the performance of model 6 in the

OLS. A description for each independent variable in the mapping algorithm, with the corresponding coefficient, standard error, and p-value.for the best model is summarised in **Table 41** to predict the EQ-5D-3L tariff score where *age* is the age of patient (18+), *primary school*, *secondary school*, and *university* are the educational level of the patient (Yes = 1, no =0), and *m_x* and *s_x* represent moderate and severe impact within FIQR 21 items (m= scores 5-6, s= scores 7-10), *item 1-21* represent FIQR 21 items (Yes = 1, no =0).

6.6.9 Validation

As the sample size is small in this database (n=160), it was difficult to split it to two datasets (estimation and validation datasets) for internal validation. Other researchers were contacted in order to obtain datasets for external validation. However, the researchers informed me that the required dataset was unavailable.

Table 41. Coefficients and summary statistics for the best performing model

Variable	Description	Coefficient	SE	p-value
Constant term	Constant term	0.504	0.197	0.012
Age	Age of patient (18+)	0.002	0.002	0.264
Primary school	Primary school degree (Yes=1, no=0)	0.03	0.046	0.519
Secondary school	Secondary school degree (Yes=1, no=0)	0.09	0.058	0.131
University	University degree (Yes=1, no=0)	-0.045	0.105	0.667
FIQR items*	(Yes=1, no=0)			
m_item 1	Moderate difficulty in brushing or combing your hair	– 0.007	0.041	0.857
s_item 1	Severe difficulty in brushing or combing your hair	– 0.003	0.049	0.938
m_item 2	Moderate difficulty with walking continuously for 20 minutes	– 0.043	0.055	0.437
s_item 2	Severe difficulty with walking continuously for 20 minutes	– 0.069	0.056	0.227
m_item 3	Moderate difficulty in preparing a homemade meal	0.059	0.054	0.284
s_item 3	Severe difficulty in preparing a homemade meal	0.001	0.061	0.985
m_item 4	Moderate difficulty with vacuuming, scrubbing or sweeping floors	– 0.044	0.086	0.613
s_item 4	Severe difficulty with vacuuming, scrubbing or sweeping floors	– 0.007	0.087	0.934
m_item 5	Moderate difficulty with lifting and carrying a bag full of groceries	0.119	0.103	0.253
s_item 5	Severe difficulty with lifting and carrying a bag full of groceries	0.183	0.113	0.108
m_item 6	Moderate difficulty with climbing one flight of stairs	– 0.116	0.089	0.194
s_item 6	Severe difficulty with climbing one flight of stairs	– 0.112	0.091	0.221
m_item 7	Moderate difficulty with changing bed sheets	0.045	0.62	0.472
s_item 7	Severe difficulty with changing bed sheets	– 0.005	0.069	0.932
m_item 8	Moderate difficulty with sitting in a chair for 45 mins	– 0.038	0.068	0.571
s_item 8	Severe difficulty with sitting in a chair for 45 mins	– 0.056	0.058	0.336
m_item 9	Moderate difficulty with going shopping for groceries	– 0.12	0.069	0.086
s_item 9	Severe difficulty with going shopping for groceries	– 0.164	0.066	0.015
m_item 10	Moderate prevention of accomplishing goals for the week	– 0.079	0.053	0.136
s_item 10	Severe difficulty preventing accomplishment of goals for the week	– 0.05	0.046	0.278
m_item 11	Moderately overwhelmed by my fibromyalgia symptoms	0.076	0.058	0.193
s_item 11	Severely overwhelmed by my fibromyalgia symptoms	0.041	0.052	0.430
m_item 12	Moderate level of pain	0.006	0.123	0.961
s_item 12	Severe level of pain	– 0.011	0.131	0.932
m_item 13	Moderate loss of energy	0.062	0.069	0.366
s_item 13	Severe loss of energy	– 0.007	0.062	0.910

Table 41 (continued)

Variable	Description	Coefficient	SE	p-value
m_item 14	Moderate level of stiffness	– 0.019	0.060	0.747
s_item 14	Severe level of stiffness	0.016	0.056	0.774
m_item 15	Moderate problems with sleep	–0.075	0.091	0.411
s_item 15	Severe problems with sleep	–0.073	0.069	0.295
m_item 16	Moderate level of depression	–0.031	0.054	0.562
s_item 16	Severe level of depression	–0.089	0.053	0.093
m_item 17	Moderate problems with memory	0.127	0.050	0.013
s_item 17	Severe problems with memory	0.113	0.052	0.031
m_item 18	Moderate level of anxiety	–0.051	0.057	0.370
s_item 18	Severe level of anxiety	–0.076	0.056	0.183
m_item 19	Moderate level of tenderness to touch	0.032	0.080	0.689
s_item 19	Severe level of tenderness to touch	0.042	0.073	0.562
m_item 20	Moderate problems with balance	0.025	0.051	0.619
s_item 20	Severe problems with balance	–0.027	0.053	0.605
m_item 21	Moderate level of sensitivity to loud noises, bright lights, odours and cold	–0.052	0.056	0.361
s_item 21	Severe level of sensitivity to loud noises, bright lights, odours and cold	–0.059	0.051	0.248

*m_item *x* indicates moderate level of scores= 5-6 on 0-10 scale, s_item *x* indicates severe level of scores=7-10 on 0-10 scale.

6.7 Discussion

6.7.1 Principal findings

To the researcher knowledge, this chapter reports the results of the first mapping study to map the widely-used measure in FM/CWP, the FIQR, onto NICE's recommended preference-based measure for economic evaluation, the EQ-5D-3L. In accordance with the NICE DSU and MAPS statements (80, 209), different regression techniques were explored to develop mapping functions and showed that it was feasible to use mapping approaches to estimate the EQ-5D-3L from the FIQR. In addition to the OLS model, which is widely used in the literature, another method for direct mapping, the CLAD model, that considers the characteristics typically seen in the distribution of the EQ-5D-3L was also applied for the FIQR. A final method was applied for response mapping of EQ-5D-3L dimension scores, the MNL model.

As the mapping measures analysed in this chapter had not been previously examined in the literature, a direct comparison of methods or results with similar mapping studies was not possible. Therefore, the findings of model performance i.e. the prediction errors were discussed in comparison with reviews or studies mapped from other disease-specific measures onto EQ-5D-3L.

Although advanced econometric models were used in this chapter to overcome the unmet assumptions of the OLS, the performance errors of CLAD models and MNL models were not found to be less than those of OLS. Particularly, the MNL was the worst performing model, while when observing the prediction ability for the observed mean and ranges of utility, the OLS outperformed other models. The mapping

algorithm (presented in section 6.7) which used the FIQR items in 3-levels and discrete-form scores, age and educational level to estimate the EQ-5D-3L index score was found to be the best model. The equation indicates that having difficulty with going shopping for groceries has the largest impact on the EQ-5D-3L index score, by -0.164 and -0.12 for severe and moderate difficulty, respectively. Less impact on the utility index is observed from having a severe level of depression (-0.089), and having a moderate level of prevention from accomplishing goals of the week (-0.079). A positive impact was observed on the EQ-5D-3L index score (0.088) from having educational level of secondary school. Lack of association was found in most variables. This lack of association may impact on the mapped scores produced by the mapping algorithm.

Mapping assumes that there is a theoretical overlap between what is being measured by the two measures. In practice, although many disease-specific measures are designed to measure different aspects of QoL, 100% overlapping with preference-based measures is not possible. On the other hand, preference-based measures are not designed to capture the important aspects of all diseases, but focus on a specific set of core health domains. For example, the EQ-5D-3L does not contain a dimension for energy. Consequently, it was not surprising in this analysis that energy in FIQR had a non-significant coefficient with the EQ-5D-3L. A low degree of overlap may affect the performance of the mapping function and this problem is most predominantly seen when mapping from condition-specific measures (86). In a review of mapping studies, the degree of error was larger when mapping from condition-specific measures (R^2 ranged from 0.17 to 0.51) compared with generic preference measures (R^2 not less than

0.51) (86). To overcome this problem, new condition-specific measures are being developed, but it is not yet clear how such measures compare with existing preference-based generic measures and whether these measures are suitable for allocation of resources (213).

As a comparison with the best performing OLS model from the analysis in this thesis, a systematic review by Brazier and colleagues (86) of 30 studies (sample size range: 68 to 23647), who performed OLS to map from disease specific measures of health to preference-based health measures, found that AD for OLS models ranged from 0.0007 to 0.042, MAE ranged from 0.0011 to 0.19, and RMSE ranged from 0.084 to 0.2. The performance statistics of the current analysis were within the range of the systematic review, but with better estimate of AD (AD=0.000, MAR=0.1279, and RMSE=0.1576 in the current analysis). Moreover, across the scale of EQ-5D-3L, the levels of performance error in low and high health states were equal to zero in MAE and RMSE, which is preferred by NICE DSU (80). Other studies found larger errors (80, 214, 215). Hawton and others, for example, mapped the Multiple Sclerosis Impact Scale onto the EQ-5D-3L and found that the MAE value was greater than 0.25 when the EQ-5D-3L utility value was less than 0.25. The results presented in this chapter indicate that there is a low tendency for the best model to over- or under-predict values for score ranges of extremely severe and mild utilities.

Regarding model selection, there is a lack of consensus in the literature regarding methods to select the best model. Most studies based the selection on a single performance measure (86, 212), in which different choices of performance criteria can

result in alternative models being selected (212). In this chapter, rather than choosing one performance statistic to select the best model, the ranked scoring method developed by Longworth and colleagues was applied (212). The ranking method is based on a system where equal weighting is given to AD, MAE, RMSE, and R^2. Ranking of performance does not consider the magnitude of prediction of the observed mean of the EQ-5D-3L, but in the present analysis the best model based on ranking was the most accurate in predicting utility index, compared to other models (section 6.3). Further research should be undertaken to test the quality of the ranking method and to incorporate the magnitude of the prediction of the observed EQ-5D-3L into selecting the best models.

Evidence found that variations in methods of mapping lead to variations in estimates of cost effectiveness (82, 216). Pennington and others, for example, examined the cost-effectiveness of disease-modifying antirheumatic medications in rheumatoid arthritis using 24 mapping algorithms that map the Health Assessment Questionnaire onto EQ-5D-3L. The analysis found that utilities produced by the algorithms were different (ranging from 2.13 to 5.65 QALYs), and that the previous NICE's decisions could be changed according to these findings (82). Therefore, it is essential for researchers to follow the recommendation of guidelines in mapping techniques to reduce the variation in the produced equations.

6.7.2 Published studies in mapping from FIQR to EQ-5D

To date, no study has mapped from the FIQR to the EQ-5D-3L. Collado-Mateo and others have mapped from the FIQR to the newer version of the EQ-5D, the EQ-5D-

5L(87), using double mapping methods. The mapping sample was Spanish women with a diagnosis of fibromyalgia, using the ACR 1990 (n=191) criteria. The mapping approach was limited to direct mapping using the OLS and GLM, with two specifications: first, the total FIQR score, second, the three domains of the FIQR. Goodness of fit was expressed by MAE, and RMSE.

Regarding the mapping to EQ-5D-5L, The GLM model (using FIQR total score) performed best compared with OLS, with the lowest error statistics (MAE = 0.137; RMSE = 0.174). The mean mapped utility (0.49) was identical to the observed utility, but under-prediction and over-prediction in the mapped utility range (0.011 to 0.870) were found (observed utility range = -0.480 to 1).

Although Collado-Mateo and colleagues mapped FIQR into EQ-5D-5L, many limitations were observed. Firstly, age was the only tested variable in the regression analysis. It is recommended that the inclusion of sociodemographic or clinical variables in the regression would control for more factors that would influence quality of life. In the presented results in this chapter, all variables were tested in the backward stepwise regression, and age and educational level were significant. Secondly, the sample was females only, in which the application of the mapping equation to male patients with FM is inapplicable. Thirdly, the Spanish value sets of EQ-5D-5L at the time of publishing the study were not available. Instead, interim values for the EQ-5D-5L were only available from a mapping study from the EQ-5D-3L (217), which is subject to uncertainty. Mapping FIQR onto the mapped version of the EQ-5D-5L tariff is called “double mapping”. Double mapping is an alternative method where it has not

been possible to obtain a sample that contains both the source and target measures (218). This method involves one estimation sample to map from the source to an intermediary measure and a second estimation sample to map from the intermediary measure onto the target measure (218). Estimates produced by double mapping should be treated with caution, as mapping twice is likely to increase the errors and uncertainty around the mapped EQ-5D-5L estimates (218). Future economic analysis based on Collado-Mateo et al.'s mapping study should fully take into account the uncertainty produced by double mapping. Moreover, once the Spanish value sets of EQ-5D-5L are available, the validation of the mapping equation is highly necessary to eliminate the unwarranted uncertainty produced by the double mapping methods.

6.7.3 Strengths and weaknesses

One of the strengths of this stage of the study is that it follows the recommendations of NICE DSU and MAPS in the methods and reporting the results (80, 218). In addition, different mapping models, addressing the characteristics of the data, and econometric approaches (i.e. direct and response mapping) were undertaken. Finally, when including multiple sociodemographic or clinical variables in the regression to improve the prediction of the model, the generalisability of the mapping equation might be restricted to only those studies that recorded the same variables along with the FIQR. The analysis of this chapter found that age and educational levels were significant variables, among others. The inclusion of these two variables has improved the models (models 2-6 and 8-12) when compared to models 1 and 7. Both variables are basic demographic data that can be found in most studies, in which the limitation from not

using the presented mapping algorithm to map between FIQR to EQ-5D-3L was reduced.

There are limitations within this mapping study. First, the present study was based on a sample of Spanish patients, and caution should be exercised when applying the mapping equation to estimate utilities of other patient populations. Second, when considering the development of mapping functions, size of the sample may be considered a key factor to produce a reliable mapping equation. In the present study, the sample size was small (n=160). However, there are no rules for sample sizes in mapping guidelines or the literature (83, 209, 210). In a review that included ninety mapping studies (sample size range= 48-134269), it was found that 21 algorithms (17%) were estimated using fewer than 200 observations (84). Thirdly, the independent variables included in the recommended mapping equation were the FIQR items, age and the educational level of the patient. Given that the number of independent variables involved in the mapping algorithm is not small, using other models analysed in this chapter with fewer variables may be seen as more practical; however, the performance would be lower than that of the recommended model. A final limitation was that a validation in an external sample or in half of the current sample was not performed, as the sample size was considered insufficient. It has been noted, however, that external validation does not often lead to any reduction in model performance (86)

6.8 Conclusion

With the significant increase in the use of economic evaluations for funding, this chapter has presented the best equation to map the FIQR onto EQ-5D-3L when measures of health-related quality of life are not available in the trial, and to inform the allocation of scarce resources. Moreover, it allows the quality of life attributable to FM/CWP to be directly compared with other diseases. Further work is needed in order to validate the mapping equation produced in this chapter

Chapter 7. Thesis discussion

7.1 Introduction

This chapter summarises and discusses the results presented in Chapters 3 to 6, to conclude how successful the thesis was in meeting its aims and objectives. The implications of these findings for policy and practice, patients and research are presented. The final section includes recommendations for future work

7.2 Summary of key findings

There are known methodological challenges in evaluating complex interventions such as PMSs, and the MRC recommends an iterative, cyclical and phased approach of feasibility work for initial evaluation before conducting a definitive RCT (116). This should involve a feasibility work to identify key uncertainties in the design and assessment of the intervention and its evaluation. Therefore, a programme of feasibility work was performed in this PhD for the evaluation of PMSs to manage people with FM/CWP in preparation for the conduct of a future definitive evaluation. This was performed by conducting a systematic review (Chapter Three), followed by a feasibility observational study (Chapter Four), then economic modelling of the lifetime indicative cost-effectiveness of PMS for people with FM/CWP (Chapter Five), and concluded with a statistical mapping study of the FIQR to the EQ-5D-3L (Chapter Six).

The sample size of the recruited FM/CWP patients in the study presented in Chapter Four was small (n=10), in which it was not possible to determine a recommendation for a future definitive trial of PMSs to manage FM/CWP. However, the research has

made a contribution to knowledge in the field and has identified important factors to be considered in planning future RCT research which can save on costs for future studies.

As none of the retrieved six economic evaluations in PMSs for FM/CWP in the systematic review (Chapter 3) met all the CHEERS quality criteria, thus it was difficult to draw an overall conclusion about the cost-effectiveness. Moreover, the MRC do not recommend performing a definitive RCT to evaluate the cost-effectiveness before performing a feasibility work. In addition, the economic evaluation studies in the review were performed with a time horizon of not more than two years. For the three aforementioned reasons, a lifetime indicative evaluation was performed (Chapter Five) through the use of an economic modelling technique and published estimates of effectiveness and cost. The model suggested that PMS intervention was found to have yielded a greater improvement of QALYs, with an average lifetime increment of 15.2 QALYs compared with SC, with a lifetime incremental cost of -£10433.
The sensitivity analysis showed that the main results were robust. This theoretical finding suggested that implementing PMSs for people with FM/CWP can lead to a significant health gain and cost saving to the NHS.

With the significant increase in the use of economic evaluations for funding and the recommendation by the MRC to perform economic evaluation for complex interventions when possible (116), the work presented in the statistical mapping chapter (Chapter Six) has presented the first mapping equation to map the widely-used disease-specific health status measure in FM, the FIQR onto EQ-5D-3L. The equation can be implemented when EQ-5D-3L data are not available in the trial in order to

inform the allocation of scarce resources in FM/CWP research including PMSs research.

In summary, the work performed in Chapters 3-6 provides an example of how to conduct a programme of feasibility work in preparation for the conduct of a definitive RCT in an already established complex intervention. Information regarding the development of such complex intervention in a health service is out of the scope of this thesis and the required information can be found in the MRC framework for the development and evaluation of complex interventions (116). The strength and weaknesses of this PhD are discussed below.

7.2 Strength and weakness

7.3.1 Strengths

Firstly, the decision analysis model methods used in this thesis were applied to a disease area for which a decision analysis model had never been applied to evaluate PMS; this economic analysis is the first study to model the life-time effectiveness and cost of PMS on patients with FM/CWP. All previously published studies were limited to a duration of two years. Secondly, it should be borne in mind that 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 sufficiently timely evidence to support decision-making. It has long been recognized that economic evaluation should be iterative, generating progressively firmer estimates of cost-effectiveness and helping to maximize the efficiency of health care research and development, while still allowing the best evidence available at any one time to

support decision-making (219). Thirdly, the decision analytic model in this thesis has been synthesized using the highest-quality data available from the fewest sources necessary to create a valid, streamlined model; this includes utility values specific to FM/CWP patients and not the general population, cost data that were validated with experts in the field, and transitional probabilities gathered from FM/CWP patient-level data of a published study. Thus, although these findings were indicative, the results from Chapter Five provide a transparent answer for decision makers regarding expanding these services in future.

Regarding the results of mapping to EQ-5D-3L from the FIQR, advanced methods of modelling were performed with a consideration to overcome the limitations of OLS using CLAD methods. In addition, in the mapping equation presented in Chapter Six, age and educational levels were the most significant covariates associated with EQ-5D-3L. Both are basic demographic data that can be found in most, if not all, studies. Therefore, the possible restriction from not applying the proposed mapping algorithm was lowered.

7.2.2 Weakness

The findings of this thesis should be carefully considered in context of its limitations. In terms of feasibility study design, there were several limitations. Firstly, the study was performed in a community-based setting, in which the results are not generalizable to other settings. Secondly, the number of people with FM/CWP referred to the PMS was low (potential reasons were discussed in Chapter Four), which affected many key

aspects of this thesis, including the sample size in the feasibility study (Chapter Four), the effectiveness of Nottingham PMSs (Chapter Four), and the required data inputs for the decision analysis model (Chapter Five). However, the amendments to methods used in Chapter Four improved the recruitment and maximised the retention of people with FM/CWP in the feasibility study. Moreover, the absence of missing data in the filled in questionnaires might suggest that all questionnaires were acceptable to the patients. Thirdly, the study may be prone to attrition bias, as the study' non-completers were those with the worst health outcomes at baseline.

With regard to the economic evaluation, the effectiveness of the PMS was derived from the study by Luciano and others, which may underestimate the effectiveness of the service in Nottingham, as tailored interventions have been shown to be more effective compared with standardised intervention in FM/CWP (6, 170-172).

In the mapping chapter, a universal weakness in the OLS is the over-prediction for severe EQ-5D-3L health states; however, the use of other mapping models does not seem to improve the predictability for all health states. A final limitation was that the validation of the mapping equation developed in Chapter Six in another sample, external validation, or in half of the original sample, internal validation, was not performed in this case, as the sample size was considered insufficient. However, it has been noted that external validation in other samples does not often lead to any reduction in model performance (86).

7.3 Implications

The results of this thesis have several important implications for policy and practice, patients and research:

7.4.1 Implications for policy and practice

Cost-effectiveness analysis is an important decision-making tool for commissioners and policy makers, yet reliable cost-effectiveness data are lacking for PMS interventions. However, the indicative economic evaluation in Chapter Six suggest that PMS might improve quality of life with reduced healthcare costs for managing people with FM or CWP (probability of 97% CE at the NHS WTP), suggesting that the widespread implementation of the PMS pathway is justified and should be made a priority by the commissioners and decision makers.

Expanding the PMS service will support the previous national calls mentioned in Chapter Two, which advocated that pain management is a strategic priority but acknowledged that the existing services were inadequate and understaffed (112, 113, 220, 221). Furthermore, as pain is more prevalent with advanced age (222), it needs to be taken into account that UK Government research has identified that the population group aged 65 and over is predicted to double by 2050 (223). Thus, if the existing resources remain unchanged, the government will not be able to provide services for any future increase in the number of people living with chronic pain (224). The findings in this study provide evidence about the cost effectiveness of PMS for the commissioners and decision makers in order to widely implement and meet the standards of these services.

In addition, looking at the high prevalence of FM/CWP and its massive impact on life and healthcare services, FM/CWP can be considered to be a significant public health problem. Early diagnosis and immediate, intensive, intervention in FM/CWP are increasingly suggested to be substantial factors to prevent the development of persistent pain and long-term dysfunction, and thus the effectiveness of the interventions might increase (225-227). Wide implementation of these services in the primary care sector would shorten the waiting time for referral and accelerate the management of FM/CWP and that of other chronic pain patients. Therefore, expanding these services should be a priority.

The application of the service in the community care setting will be in line with the current commissioning preference to transfer the management of long-term conditions back into the community. Moreover, pain management services in the community have good links with other community services, aiding liaison and support for self-management; thus, placing the service in the community will deliver the quality standards of the National Service Framework for Long Term Conditions (228). On the international level, many guidelines advocate the use of PMS intervention to manage chronic pain. The analysis of this study provides compelling evidence to encourage its implementation at the global level.

From the Nottingham experience with PMS and SC pathways, Hobbs and colleagues found that approximately 90% of referrals to secondary care in the SC pathway were inefficient in Nottingham (115). In regard to the PMS pathway, they emphasized the advantage of obtaining a tailored management in a timely manner at an accessible

location, in which early comprehensive and individualised PMS has a potential for a better success rate on patients(115). Where there is evidence suggesting the biopsychosocial model for managing other chronic pain conditions such as low back pain, consideration should be given to expanding the PMS to manage other chronic pain conditions.

7.4.2 Implications for patients

Patients' need for more services was investigated in the National Pain Audit survey that ran from 2009-2013 (220, 229). The survey included 10,000 patient questionnaires covering patients' health states and experiences of pain services in England and Wales. The audit found that the pain services were delivering care to a group of people who reported a very poor quality of life, with a mean of 0.4 on the EQ-5D-3L. This score is on a par with people suffering with advanced senility and lower than that of many individuals with other long term conditions (220, 229). Although the audit found that less than half of clinics were fulfilling the minimum requirement for staffing and competencies, as defined by the presence of a physician, physiotherapist and psychologist, about half of the respondents had improved their overall quality of life, and 76% reported improvement specifically in pain-related quality of life after six months of receiving care. If the policy makers support these services to meet the standards, the percentage of patients with improved quality of life could be higher.

The implementation of well-staffed primary care-based pain management services is likely to increase patients' uptake of the PMS service for many reasons: 1) a more effective management plan, 2) easy access, 3) eliminating the burden of transportation

to secondary services, 4) shorter waiting times than for secondary care. In addition, these services will provide the patients with an opportunity to share their experiences and support each other through the FM/CWP groups. A previous study found that the social interaction of patients with one another has a vital impact on self-esteem and confidence (150).

7.4.3 Implications for research

As pointed out above, the systematic review in Chapter Four identified many drawbacks in the included studies, including the difficulty in drawing a conclusion about the cost-effectiveness of PMS in managing FM/CWP and great variability of the interventions, outcomes, and study durations. The major limitation observed was that the methodological quality of most studies included was low. The review highlighted key design areas that researchers need to consider when conducting economic evaluations, including following standard design guidelines. However, the cost-effectiveness over longer periods of time (follow-up of more than two years) needs further investigation, and it is likely that this will require the use of routinely collected data and more extensive use of economic evaluation modelling approaches.

Chapter Five reported the economic evaluation of the PMS compared to SC. It was found that the estimated cost-effectiveness was most influenced by discount rate (0 to 6%) and the utility of mild cases when varied to Schaefer et al.'s utilities (187) in the one-way sensitivity analysis (187). The QALY gain significantly increased by 3.1 QALYs by varying the mild utility in the model. Thus, future research which addresses this factor is required.

The mapping technique used in this thesis offers an equation to elicit the EQ-5D-3L utility index score from the FIQR when data for the EQ-5D has not been directly collected in a study, including RCTs (196). Hence, this mapping equation will allow researchers to perform economic evaluations, specifically cost-utility analysis, and permit NICE and other decision makers to compare the results of other health technologies applied either in fibromyalgia or different diseases.

7.5 Future recommendations

The systematic review presented in Chapter Three suggests that future studies evaluating the cost-effectiveness of pain management services must follow the clinical and quality criteria listed in guidelines such as the CHEERS guidelines (230). Another finding is that all published studies which evaluate the cost-effectiveness of PMS were implemented within no longer than two years of follow-up. Thus, data on the long term benefit and cost of these services are lacking. Longer follow-up studies of more than two years are needed to determine the effectiveness, cost, and incremental cost-effectiveness of PMSs. An observational study design as recommended by the MRC could provide an answer (116).

Findings from the feasibility study in Chapter Four suggest that future qualitative studies that aim to explore the barriers and facilitators to participation of chronic pain patients in research are vital. In addition, interviewing participants, clinicians who are recruiting to the study or the therapists delivering the interventions can provide valuable information regarding the acceptability and the suitability of the intervention.

These data will increase our understanding of the optimal strategy to recruit patients with FM/CWP and deliver interventions.

Many studies in the literature report that recruiting and retaining participants is a major difficulty in research (150-152). From the experience gained in this work, although the retention rate at six months was 80%, it can be observed that patients who fail to be retained at the six-month follow-up were having severe health outcomes at baseline when compared with patients who completed the study. In addition, patients who did not participate in the study reported that severe pain and time commitment were the main factors affecting their participation. Both factors are well-documented in the literature as barriers for participation in research (231-233). Future studies need to consider engaging people with FM/CWP in the study design by having PPI representatives. Evidence suggest that PPIs can provide a substantial insights on retaining very advanced stages of lung cancer patients by involving patients carers as a proxy for the patient (234).

After increasing the number of PMSs to enhance the number of patients recruited to the study and performing a qualitative research study to understand the facilitators and barriers of recruitment of people with FM/CWP into research, the best proposed method for a definitive economic evaluation of PMSs is through a multi-centre, pragmatic cluster RCTs and economic evaluation with qualitative process evaluation. The proposed mixed method design with economic modelling of long-term effects is recommended by the MRC to evaluate complex interventions (116). The description for each method is presented below.

In regard to the proposed quantitative trial, the main aim of the trial is to evaluate the effectiveness and cost-effectiveness of PMSs compared with SC, from the perspective of NHS England, through a pragmatic cluster RCT. The pragmatic approach evaluates the PMS and SC intervention in a manner that would reflect as closely as possible the conditions of daily medical practice and retain the randomisation concept with minimised bias (135). This method offers fewer restrictions in how patients are recruited and followed after randomisation, thus maximising the external validity. In complex intervention trials, in which blinding the intervention is often impossible, the pragmatic RCT design is a suitable method (235). According to the MRC guidance for evaluating complex interventions (116), patient level RCTs are usually not practical, due to the possibility of contamination between the intervention and the control arm. Therefore, in order to address the limitation of patient level RCT, cluster RCT might be considered to assess the effectiveness of a complex intervention such as PMS. The advantage of cluster RCT over patient level RCT is that cluster RCT can account for the contamination within the cluster. In addition, cluster RCTs are suitable for assessing healthcare services addressing behavioural aspects of patient care (236).

In regard to the proposed economic modelling method, long-term follow-up is a general problem associated with using trials. Therefore, long term modelling analysis can be performed after a definitive economic evaluation to provide an answer about the lifetime cost and health benefit of PMS compared with SC from the perspective of NHS England.

In regard to the proposed qualitative process evaluation, many aims can be investigated during or after the quantitative trial (237) such as to: examine whether the PMS was delivered as intended; describe processes of implementation and change; explore the experiences of HCPs and patients participating in PMS; explore reasons for the findings of the quantitative trial, explain variations in effectiveness within the sample, or to generate further questions or hypotheses (237).

Many studies which have undertaken the previous recommended pragmatic RCT for economic evaluation of complex interventions in chronic pain conditions or other conditions are successful examples for using such a method (151, 238-243). Another successful study performed to evaluate complex interventions in chronic pain patients in the UK with mixed methods i.e. qualitative work with a quantitative study, without economic evaluation (244). The study by Hadi and colleagues evaluated a pharmacist and nurse-led clinic using a quasi-experimental study combined with qualitative interviews. The quasi-experimental design in Hadi et al.'s study used a single-group pretest-posttest approach. The author highlighted the impracticality of identifying people receiving "standard care" through GPs, as there is currently no mechanism to identify people receiving standard care from GPs' systems (244). The study design used by Hadi et al. (244) and the justification of assessing the PMS arm only is similar to the study design and justification used in the feasibility study presented in Chapter Four. Both Hadi et al.'s study and this study were aiming to assess the effectiveness of a complex intervention based on MRC guidance. While Hadi et al. used qualitative and quantitative study design with a focus on patients' perspective, by conducting qualitative interviews, the present study addressed 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.

Further recommendation from the analysis of the indicative economic evaluation presented in Chapter Five is that there is a need for future studies of utility estimate for mild FM/CWP, as this parameter had the most effect on the ICER. Additional data on this parameter will add to the robustness of future models evaluating clinical and economic outcomes of PMS for FM/CWP.

Final recommendations arising from the mapping from FIQR to EQ-5D-3L is that further research is desirable to verify the mapping equation presented in Chapter Six. Moreover, the most common methods for direct (OLS and CLAD) and response mapping (MNL) were utilised in this thesis. It is recommended that future mapping studies investigate alternative regression models when mapping from the FIQR to the EQ-5D-3L, to provide comparative results with the algorithm presented in this thesis.

7.6 Conclusions

This thesis has adhered to current guidance provided by the MRC to evaluate PMSs. The indicative cost effectiveness of PMSs was investigated suggesting that PMSs could improve patient outcomes and be cost-saving to the NHS. Key methodological elements for further evaluation of PMSs in clinical trials were identified. Although this PhD has estimated the indicative cost-effectiveness and based on that recommendations can be made for wider implementation of the service, a future randomised trial, with associated long-term follow-up will provide definitive evidence about the cost-effectiveness of PMSs in managing people with FM/CWP. This research has provided the support for continuous funding and wider implementation of PMS pathway in the UK and worldwide.

The mapping model using OLS regression showed a reasonable predictive ability. This mapping algorithm enables researchers to convert results from the FIQR to the EQ-5D-3L utility indexes for people with FM/CWP. Nevertheless, using OLS regression to predict very low and high EQ-5D indices remains challenging. This finding can help when evaluating the cost-utility analysis of healthcare interventions in FM/CWP patients.

References

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990;33(2):160-72.

2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008;58(1):26-35.

3. Branco JC, Bannwarth B, Failde I, Abello Carbonell J, Blotman F, Spaeth M, et al. Prevalence of fibromyalgia: a survey in five European countries. Semin Arthritis Rheum. 2010;39(6):448-53.

4. Papageorgiou AC, Silman AJ, Macfarlane GJ. Chronic widespread pain in the population: a seven year follow up study. Ann Rheum Dis. 2002;61(12):1071-4.

5. Croft P, Schollum J, Silman A. Population study of tender point counts and pain as evidence of fibromyalgia. BMJ. 1994;309(6956):696-9.

6. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2016.

7. Papadopoulou D, Fassoulaki A, Tsoulas C, Siafaka I, Vadalouca A. A meta-analysis to determine the effect of pharmacological and non-pharmacological treatments on fibromyalgia symptoms comprising OMERACT-10 response criteria. Clin Rheumatol. 2016;35(3):573-86.

8. Sommer C, Hauser W, Alten R, Petzke F, Spath M, Tolle T, et al. [Drug therapy of fibromyalgia syndrome. Systematic review, meta-analysis and guideline]. Schmerz. 2012;26(3):297-310.

9. Burckhardt C, Goldenberg D, Crofford L, Gerwin R, Gowans S, Jackson K, et al. Guideline for the management of fibromyalgia syndrome pain in adults and children. APS clinical practice guidelines series. 2005(4).

10. Fitzcharles M-A, Ste-Marie PA, Goldenberg DL, Pereira JX, Abbey S, Choinière M, et al. 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. Pain Research and Management. 2013;18(3):119-26.

11. Sarzi-Puttini P, Atzeni F, Mease P. Chronic widespread pain or fibromyalgia? That is the question. Best Practice & Research: Clinical Rheumatology. 2011;25(2):131-2.

12. Cohen H. Controversies and challenges in fibromyalgia: a review and a proposal. Therapeutic Advances in Musculoskeletal Disease. 2017;9(5):115-27.

13. McNally JD, Matheson DA, Bakowsky VS. The epidemiology of self-reported fibromyalgia in Canada. Chronic diseases in Canada. 2006;27(1):9-16.

14. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. Best Practice & Research Clinical Rheumatology. 2007;21(3):403-25.

15. Weir PT, Harlan GA, Nkoy FL, Jones SS, Hegmann KT, Gren LH, et al. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. J Clin Rheumatol. 2006;12(3):124-8.

16. Rahman A, Underwood M, Carnes D. Fibromyalgia. BMJ. 2014;348.

17. Ablin J, Neumann L, Buskila D. Pathogenesis of fibromyalgia - A review. Joint Bone Spine. 2008;75(3):273-9.

18. Bellato E, Marini E, Castoldi F, Barbasetti N, Mattei L, Bonasia DE, et al. Fibromyalgia Syndrome: Etiology, Pathogenesis, Diagnosis, and Treatment. Pain Research and Treatment. 2012;2012:426130.

19. Choy E, Perrot S, Leon T, Kaplan J, Petersel D, Ginovker A, et al. A patient survey of the impact of fibromyalgia and the journey to diagnosis. BMC Health Services Research. 2010;10(1):102.

20. Ullrich A, Farin E, Jackel WH. [Restrictions in participation in women with fibromyalgia syndrome. An explorative pilot study]. Schmerz. 2012;26(1):54-60.

21. Adams EH, McElroy HJ, Udall M, Masters ET, Mann RM, Schaefer CP, et al. Progression of fibromyalgia: results from a 2-year observational fibromyalgia and chronic pain study in the US. Journal of Pain Research. 2016;9:325-36.

22. White KP, Harth M. Classification, epidemiology, and natural history of fibromyalgia. Curr Pain Headache Rep. 2001;5.

23. Dreyer L, Kendall S, Danneskiold-Samsøe B, Bartels EM, Bliddal H. Mortality in a cohort of Danish patients with fibromyalgia: increased frequency of suicide. Arthritis & Rheumatism. 2010;62(10):3101-8.

24. Wolfe F, Hassett AL, Walitt B, Michaud K. Mortality in fibromyalgia: a study of 8,186 patients over thirty-five years. Arthritis care & research. 2011;63(1):94-101.

25. Nock MK, Hwang I, Sampson N, Kessler RC, Angermeyer M, Beautrais A, et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO World Mental Health Surveys. PLoS med. 2009;6(8):e1000123.

26. Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. Molecular psychiatry. 2010;15(8):868-76.

27. Fishbain DA, editor The association of chronic pain and suicide. Seminars in clinical neuropsychiatry; 1999.

28. Tang NK, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. Psychological medicine. 2006;36(05):575-86.

29. Goodwin RD, Marusic A. Association between short sleep and suicidal ideation and suicide attempt among adults in the general population. Sleep. 2008;31(8):1097-101.

30. Wojnar M, Ilgen MA, Wojnar J, McCammon RJ, Valenstein M, Brower KJ. Sleep problems and suicidality in the National Comorbidity Survey Replication. Journal of psychiatric research. 2009;43(5):526-31.

31. Wolfe F, Hassett AL, Walitt B, Michaud K. Mortality in fibromyalgia: A study of 8,186 patients over thirty-five years. Arthritis care & research. 2011;63(1):94-101.

32. Calandre EP, Vilchez JS, Molina-Barea R, Tovar MI, Garcia-Leiva JM, Hidalgo J, et al. Suicide attempts and risk of suicide in patients with fibromyalgia: a survey in Spanish patients. Rheumatology. 2011;50(10):1889-93.

33. Yilmaz F, Sahin F, Ergoz E, Deniz E, Ercalik C, Yucel SD, et al. Quality of life assessments with SF 36 in different musculoskeletal diseases. Clin Rheumatol. 2008;27(3):327-32.

34. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. Health Qual Life Outcomes. 2008;6(8):1477-7525.

35. Birtane M, Uzunca K, Tastekin N, Tuna H. The evaluation of quality of life in fibromyalgia syndrome: a comparison with rheumatoid arthritis by using SF-36 Health Survey. Clin Rheumatol. 2007;26(5):679-84.

36. Hoffman DL, Dukes EM. The health status burden of people with fibromyalgia: a review of studies that assessed health status with the SF-36 or the SF-12. Int J Clin Pract. 2008;62(1):115-26.

37. Salaffi F, Girolimetti R, Atzeni F, Gasparini S, Grassi W. Health-related quality of life in fibromyalgia patients: a comparison with rheumatoid arthritis patients and the general population using the SF-36 health survey. Clinical & Experimental Rheumatology. 2009;27(5):S67.

38. Wolfe F, Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize ra patients with fibromyalgia. J Rheumatol. 2004;31(4):695-700.

39. Grodman I, Buskila D, Arnson Y, Altaman A, Amital D, Amital H. Understanding fibromyalgia and its resultant disability. Isr Med Assoc J. 2011;13(12):769-72.

40. Mannerkorpi K, Gard G. Hinders for continued work among persons with fibromyalgia. BMC Musculoskelet Disord. 2012;13(96):1471-2474.

41. White LA, Birnbaum HG, Kaltenboeck A, Tang J, Mallett D, Robinson RL. Employees with fibromyalgia: medical comorbidity, healthcare costs, and work loss. J Occup Environ Med. 2008;50(1):13-24.

42. Henriksson CM, Liedberg GM, Gerdle B. Women with fibromyalgia: work and rehabilitation. Disabil Rehabil. 2005;27(12):685-94.

43. Al-Allaf AW. Work disability and health system utilization in patients with fibromyalgia syndrome. J Clin Rheumatol. 2007;13(4):199-201.

44. Kurtze N, Gundersen KT, Svebak S. The impact of perceived physical dysfunction, health-related habits, and affective symptoms on employment status among fibromyalgia support group members. Journal of musculoskeletal pain. 2001;9(2):39-53.

45. Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. Arthritis Rheum. 1997;40(9):1560-70.

46. Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Claxton AJ. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. J Rheumatol. 2003;30(6):1318-25.

47. Hughes G, Martinez C, Myon E, Taieb C, Wessely S. The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice. Arthritis Rheum. 2006;54(1):177-83.

48. Haviland MG, Banta JE, Przekop P. Hospitalisation charges for fibromyalgia in the United States, 1999-2007. Clin Exp Rheumatol. 2012;30(6 Suppl 74):129-35.

49. Knight T, Schaefer C, Chandran A, Zlateva G, Winkelmann A, Perrot S. Health-resource use and costs associated with fibromyalgia in France, Germany, and the United States. Clinicoecon Outcomes Res. 2013;5:171-80.

50. Wolfe F, Clauw DJ, Fitzcharles M, Goldenberg DL, Katz RS, Mease P, et al. The american college of rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res. 2010;62.

51. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011;38(6):1113-22.

52. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Seminars in Arthritis and Rheumatism. 2016;46(3):319-29.

53. Glennon P. Fibromyalgia syndrome: management in primary care. Rep Rheum Dis. 2010;6:1-6.

54. Bennett RM. Clinical manifestations and diagnosis of fibromyalgia. Rheum Dis Clin North Am. 2009;35(2):215-32.

55. Fitzcharles MA, Boulos P. Inaccuracy in the diagnosis of fibromyalgia syndrome: analysis of referrals. Rheumatology (Oxford, England). 2003;42(2):263-7.

56. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res. 2010;62(5):600-10.

57. Wolfe F. New American College of Rheumatology Criteria for Fibromyalgia: A Twenty-Year Journey. Arthritis care & research. 2010;62(5):583-4.

58. Hayes SM, Myhal GC, Thornton JF, Camerlain M, Jamison C, Cytryn KN, et al. Fibromyalgia and the therapeutic relationship: where uncertainty meets attitude. Pain Res Manag. 2010;15(6):385-91.

59. Clark P, Paiva ES, Ginovker A, Salomon PA. A patient and physician survey of fibromyalgia across Latin America and Europe. BMC Musculoskelet Disord. 2013;14(188):1471-2474.

60. Perrot S, Choy E, Petersel D, Ginovker A, Kramer E. Survey of physician experiences and perceptions about the diagnosis and treatment of fibromyalgia. BMC Health Services Research. 2012;12(1):356.

61. Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, et al. Fibromyalgia syndrome module at OMERACT 9: domain construct. J Rheumatol. 2009;36(10):2318-29.

62. Bennett R, Friend R, Jones K, Ward R, Han B, Ross R. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Research & Therapy. 2009;11(4):R120.

63. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

64. Jensen MP, Turner JA, Romano JM. What is the maximum number of levels needed in pain intensity measurement? Pain. 1994;58(3):387-92.

65. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain. 1983;16(1):87-101.

66. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23(2):129-38.

67. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975;1(3):277-99.

68. Smets E, Garssen B, Bonke Bd, De Haes J. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. Journal of psychosomatic research. 1995;39(3):315-25.

69. Stewart AL, Ware JE. Measuring functioning and well-being: the medical outcomes study approach: duke university Press; 1992.

70. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.

71. Seidenberg M, Haltiner A, Taylor MA, Hermann BB, Wyler A. Development and validation of a Multiple Ability Self-Report Questionnaire. J Clin Exp Neuropsychol. 1994;16(1):93-104.

72. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

73. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clinical and experimental rheumatology. 2005;23(5):S154.

74. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. Journal of Rheumatology. 1991;18(5):728-33.

75. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.

76. US Department of Health and Human Services FDA Center for Drug Evaluation and Research, US Department of Health and Human Services FDA Center for Biologics Evaluation and Research, US Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006;4:79.

77. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: National Institute for Health and Clinical Excellence; 2013.

78. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-92.

79. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI®): concepts, measurement properties and applications. Health and quality of life outcomes. 2003;1(1):54.

80. Brazier J, Longworth L. NICE DSU technical support document 8: An introduction to the measurement and valuation of health for NICE submissions 2011. Available from: http://www.nicedsu.org.uk/TSD8%20Introduction%20to%20MVH_final.pdf.

81. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. NICE's Position statement on use of the EQ-5D-5L valuation set. 2017.

82. Pennington B, Davis S. Mapping from the Health Assessment Questionnaire to the EQ-5D: The Impact of Different Algorithms on Cost-Effectiveness Results. Value in Health. 2014;17(8):762-71.

83. Longworth L, Rowen D. NICE DSU Technical Support Document 10: The use of mapping methods to estimate health state utility values 2011. Available from: http://www.nicedsu.org.uk/TSD%2010%20mapping%20FINAL.pdf.

84. Dakin H. Review of studies mapping from quality of life or clinical measures to EQ-5D: an online database. Health and Quality of Life Outcomes HERC database of mapping studies2013 [Version 5.0 (Last updated: 16th May 2016). Available from: http://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies.

85. Coast J. Reprocessing data to form QALYs. BMJ. 1992;305(6845):87-90.

86. Brazier JE, Yang Y, Tsuchiya A, Rowen DL. A review of studies mapping (or cross walking) non-preference based measures of health to generic preference-based measures. The European Journal of Health Economics. 2010;11(2):215-25.

87. Collado-Mateo D, Chen G, Garcia-Gordillo MA, Iezzi A, Adsuar JC, Olivares PR, et al. "Fibromyalgia and quality of life: mapping the revised fibromyalgia impact questionnaire to the preference-based instruments". Health and Quality of Life Outcomes. 2017;15(1):114.

88. Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis. 2008;67(4):536-41.

89. Arnold LM, Gebke KB, Choy EH. Fibromyalgia: management strategies for primary care providers. Int J Clin Pract. 2016;70(2):99-112.

90. Fibromyalgia Association UK. Fibromyalgia Association UK calls for greater awareness and education to help thousands of diagnosed patients in the UK. 2014. Available from: http://www.fmauk.org/latest-news-mainmenu-2/press-releases-mainmenu-37/908-fibromyalgia-international-awareness-day-may-12.

91. Russell IJ, Larson AA. Neurophysiopathogenesis of fibromyalgia syndrome: a unified hypothesis. Rheum Dis Clin North Am. 2009;35(2):421-35.

92. Clauw DJ, Arnold LM, McCarberg BH. The science of fibromyalgia. Mayo Clin Proc. 2011;86(9):907-11.

93. Nüesch E, Häuser W, Bernardy K, Barth J, Jüni P. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. Annals of the Rheumatic Diseases. 2013;72(6):955-62.

94. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain management: past, present, and future. Am Psychol. 2014;69(2):119-30.

95. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007;133(4):581-624.

96. Allegrante JP. The role of adjunctive therapy in the management of chronic nonmalignant pain. Am J Med. 1996;101(1A):33S-9S.

97. Ablin J, Fitzcharles M-A, Buskila D, Shir Y, Sommer C, Häuser W. Treatment of Fibromyalgia Syndrome: Recommendations of Recent Evidence-Based Interdisciplinary Guidelines with Special Emphasis on Complementary and Alternative Therapies. Evidence-based Complementary and Alternative Medicine : eCAM. 2013;2013:485272.

98. Goldenberg DL. Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome. Current Opinion in Rheumatology. 1997;9(2):136-43.

99. Goldenberg DL, Bradley LA, Arnold LM, Glass JM, Clauw DJ. Understanding fibromyalgia and its related disorders. Prim Care Companion J Clin Psychiatry. 2008;10(2):133-44.

100. Seers K, Acdec W, Richardson P, Collett B. Desirable criteria for pain management programmes: report of a working party of the Pain Society of Great Britain & Ireland. 1997.

101. The British Pain Society. Guidelines for Pain Management Programmes for adults. London. 2013. Available from: www.britishpainsociety.org.

102. Medicine FoP. Core Standards for Pain Management Services in the UK (CSPMS) 2015. Available from: https://www.britishpainsociety.org.

103. Choi BC, Pak AW. Multidisciplinarity, interdisciplinarity and transdisciplinarity in health research, services, education and policy: 1. Definitions, objectives, and evidence of effectiveness. Clinical and investigative medicine Medecine clinique et experimentale. 2006;29(6):351-64.

104. Giusti EM, Castelnuovo G, Molinari E. Differences in Multidisciplinary and Interdisciplinary Treatment Programs for Fibromyalgia: A Mapping Review. Pain Research and Management. 2017;2017:19.

105. Scott CM, Hofmeyer AT. Acknowledging complexity: critically analyzing context to understand interdisciplinary research. Journal of interprofessional care. 2007;21(5):491-501.

106. Häuser W, Bernardy K, Arnold B, Offenbächer M, Schiltenwolf M. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. Arthritis care & research. 2009;61(2):216-24.

107. The International Association for the Study of Pain. Pain Clinic Guidelines 2009. Available from: https://www.iasp-pain.org/education/content.aspx?itemnumber=1471.

108. The Royal College of General Practitioners. Pain Management Services: Planning for the future 2013. Available from: http://www.rcoa.ac.uk/system/files/FPM-Pain-Management-Services.pdf.

109. Keel P. Pain management strategies and team approach. Bailliere's best practice & research Clinical rheumatology. 1999;13(3):493-506.

110. Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. Rheumatology (Oxford, England). 2008;47(5):670-8.

111. Robinson RL, Jones ML. In search of pharmacoeconomic evaluations for fibromyalgia treatments: a review. Expert Opin Pharmacother. 2006;7(8):1027-39.

112. Department of Health. 150 years of the Annual Report of the Chief Medical Officer (2008). Available from http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_096231.pdf (accessed 12 April 2017). 12 April 2017.

113. NHS Quality Improvement Scotland.Getting to GRIPS with Chronic Pain in Scotland (2nd edition July2008). Available from http://www.healthcareimprovementscotland.org/our_work/long_term_conditions/programme_resources/grips_report.aspx (accessed 12 April 2017).

114. Gilron I, Bailey J, Weaver DF, Houlden RL. Patients' attitudes and prior treatments in neuropathic pain: a pilot study. Pain Res Manag. 2002;7(4):199-203.

115. Greg Hobbs RK. Commissioning for pain management service. British Journal of Healthcare Management. 2011;17(7):302-6.

116. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance 2008. 2008;9(29): 10-52.

117. Centre for Reviews and Dissemination. Systematic review: CRD's guidance for undertaking reviews in health care. York: University of York; 2009.

118. Karjalainen K, Malmivaara A, van Tulder M, Roine R, Jauhiainen M, Hurri H, et al. Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults. Cochrane Database Syst Rev. 2000(2):CD001984.

119. Kamper SJ, Apeldoorn AT, Chiarotto A, Smeets RJEM, Ostelo RWJG, Guzman J, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. BMJ : British Medical Journal. 2015;350.

120. Deare JC, Zheng Z, Xue CC, Liu JP, Shang J, Scott SW, et al. Acupuncture for treating fibromyalgia. Cochrane Database Syst Rev. 2013;5:CD007070.

121. The Scottish Intercollegiate Guidelines Network (SIGN). Search filters 2015 [Available from: http://www.sign.ac.uk/methodology/filters.html.

122. Furlan AD, Pennick V, Bombardier C, van Tulder M. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine. 2009;34(18):1929-41.

123. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement2013 2013-03-25 11:31:35.

124. International Society For Pharmacoeconomics and Outcomes Research ISPOR. Health Economic Evaluation Publication Guidelines (CHEERS): Good Reporting Practices 2015 [Available from: http://www.ispor.org/taskforces/economicpubguidelines.asp.

125. Luciano JV, D'Amico F, Cerda-Lafont M, Penarrubia-Maria MT, Knapp M, Cuesta-Vargas AI, et al. Cost-utility of cognitive behavioral therapy versus U.S. Food and Drug Administration recommended drugs and usual care in the treatment of patients with fibromyalgia: an economic evaluation alongside a 6-month randomized controlled trial. Arthritis Res Ther. 2014;16(5):451.

126. Zijlstra TR, Braakman-Jansen LM, Taal E, Rasker JJ, van de Laar MA. Cost-effectiveness of Spa treatment for fibromyalgia: general health improvement is not for free. Rheumatology. 2007;46(9):1454-9.

127. Gusi N, Tomas-Carus P. Cost-utility of an 8-month aquatic training for women with fibromyalgia: a randomized controlled trial. Arthritis Res Ther. 2008;10(1):22.

128. Luciano JV, Sabes-Figuera R, Cardenosa E, M TP-M, Fernandez-Vergel R, Garcia-Campayo J, et al. Cost-utility of a psychoeducational intervention in fibromyalgia patients compared with usual care: an economic evaluation alongside a 12-month randomized controlled trial. Clin J Pain. 2013;29(8):702-11.

129. Goossens ME, Rutten-van Molken MP, Leidl RM, Bos SG, Vlaeyen JW, Teeken-Gruben NJ. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. II. Economic evaluation. J Rheumatol. 1996;23(7):1246-54.

130. McBeth J, Prescott G, Scotland G, Lovell K, Keeley P, Hannaford P, et al. Cognitive behavior therapy, exercise, or both for treating chronic widespread pain. Arch Intern Med. 2012;172(1):48-57.

131. Beasley M, Prescott GJ, Scotland G, McBeth J, Lovell K, Keeley P, et al. Patient-reported improvements in health are maintained 2 years after completing a short course of cognitive behaviour therapy, exercise or both treatments for chronic widespread pain: long-term results from the MUSICIAN randomised controlled trial. RMD Open. 2015;1(1).

132. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337.

133. Guy W. Clinical global impression scale. The ECDEU Assessment Manual for Psychopharmacology-Revised Volume DHEW Publ No ADM. 1976;76(338):218-22.

134. Elliott R, Payne K. Essentials of Economic Evaluation in Healthcare: Pharmaceutical Press; 2005.

135. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes: Oxford University Press. New York. 2005.

136. Petrou S, Gray A. Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting. BMJ. 2011;342.

137. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. Bmj. 2014;348:g1687.

138. Raichle KA, Osborne TL, Jensen MP, Cardenas D. The reliability and validity of pain interference measures in persons with spinal cord injury. J Pain. 2006;7(3):179-86.

139. Osborne TL, Raichle KA, Jensen MP, Ehde DM, Kraft G. The reliability and validity of pain interference measures in persons with multiple sclerosis. J Pain Symptom Manage. 2006;32(3):217-29.

140. Mendoza T, Mayne T, Rublee D, Cleeland C. Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. European journal of pain (London, England). 2006;10(4):353-61.

141. Elliott RA, Boyd MJ, Salema N-E, Davies J, Barber N, Mehta RL, et al. Supporting adherence for people starting a new medication for a long-term condition through community pharmacies: a pragmatic randomised controlled trial of the New Medicine Service. BMJ Quality & Safety. 2015;25(10): 747-58.

142. StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. 2015.

143. Tickle-Degnen L. Nuts and Bolts of Conducting Feasibility Studies. The American Journal of Occupational Therapy. 2013;67(2):171-6.

144. Field A. Discovering statistics using SPSS: Sage publications; 2009.

145. Treweek S, Lockhart P, Pitkethly M, Cook JA, Kjeldstrøm M, Johansen M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. BMJ open. 2013;3(2):e002360.

146. Bower P, Brueton V, Gamble C, Treweek S, Smith CT, Young B, et al. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. Trials. 2014;15(1):1.

147. Broom DH, Woodward RV. Medicalisation reconsidered: toward a collaborative approach to care. Sociology of Health & Illness. 1996;18(3):357-78.

148. Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, et al. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. Health Technol Assess. 2007;11(48):iii, ix-105.

149. Eborall HC, Stewart MC, Cunningham-Burley S, Price JF, Fowkes FGR. Accrual and drop out in a primary prevention randomised controlled trial: qualitative study. Trials. 2011;12(1):7.

150. Carnes D, Homer K, Underwood M, Pincus T, Rahman A, Taylor SJ. Pain management for chronic musculoskeletal conditions: the development of an evidence-based and theory-informed pain self-management course. BMJ open. 2013;3(11):e003534.

151. Lamb SE, Hansen Z, Lall R, Castelnuovo E, Withers EJ, Nichols V, et al. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. The Lancet. 2010;375(9718):916-23.

152. Johnson RE, Jones GT, Wiles NJ, Chaddock C, Potter RG, Roberts C, et al. Active exercise, education, and cognitive behavioral therapy for persistent disabling low back pain: a randomized controlled trial. Spine. 2007;32(15):1578-85.

153. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise Therapy for Fibromyalgia. Current Pain and Headache Reports. 2011;15(5):358-67.

154. Kroese ME, Severens JL, Schulpen GJ, Bessems MC, Nijhuis FJ, Landewe RB. Specialized rheumatology nurse substitutes for rheumatologists in the diagnostic process of fibromyalgia: a cost-consequence analysis and a randomized controlled trial. J Rheumatol. 2011;38(7):1413-22.

155. Arnold LM, Crofford LJ, Mease PJ, Burgess SM, Palmer SC, Abetz L, et al. Patient perspectives on the impact of fibromyalgia. Patient education and counseling. 2008;73(1):114-20.

156. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. Health and Quality of Life Outcomes. 2008;6(1):8.

157. Kroese M, Schulpen G, Bessems M, Nijhuis F, Severens J, Landewe R. The feasibility and efficacy of a multidisciplinary intervention with aftercare meetings for fibromyalgia. Clin Rheumatol. 2009;28(8):923-9.

158. Burckhardt CS. Nonpharmacologic management strategies in fibromyalgia. Rheumatic disease clinics of North America. 2002;28(2):291-304.

159. van Eijk-Hustings Y, Kroese M, Tan F, Boonen A, Bessems-Beks M, Landewé R. Challenges in demonstrating the effectiveness of multidisciplinary treatment on quality of life, participation and health care utilisation in patients with fibromyalgia: a randomised controlled trial. Clinical rheumatology. 2013;32(2):199-209.

160. Walters SJ, Bonacho dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ open. 2017;7(3).

161. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling Good Research Practices—Overview: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Value in Health. 2012;15(6):796-803.

162. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. Med Decis Making. 2012;32(5):690-700.

163. Vemer P, Corro Ramos I, van Voorn GA, Al MJ, Feenstra TL. AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users. Pharmacoeconomics. 2016;34(4):349-61.

164. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press; 2006.

165. Choy E, Richards S, Bowrin K, Watson P, Lloyd A, Sadosky A, et al. Cost effectiveness of pregabalin in the treatment of fibromyalgia from a UK perspective. Curr Med Res Opin. 2010;26(4):965-75.

166. Arreola Ornelas H, Rosado Buzzo A, Garcia L, Dorantes Aguilar J, Contreras Hernandez I, Mould Quevedo JF. Cost-effectiveness analysis of pharmacologic treatment of fibromyalgia in Mexico. Reumatol Clin. 2012;8(3):120-7.

167. Beard SM, Roskell N, Le TK, Zhao Y, Coleman A, Ang D, et al. Cost effectiveness of duloxetine in the treatment of fibromyalgia in the United States. Journal of Medical Economics. 2011;14(4):463-76.

168. TreeAge Pro 2015, R1.0. TreeAge Software, Williamstown, MA. Software available at https://www.treeage.com

169. Lan Chen-Chia, Tseng Chun-Hung, Chen Jiunn-Horng, Lan Joung-Liang, Wang Yu-Chiao, Tsay Gregory J, et al. Increased risk of a suicide event in patients with primary fibromyalgia and in fibromyalgia patients with concomitant comorbidities: A nationwide population-based cohort study. Medicine. 2016;95(44):e5187.

170. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA. 2004;292(19):2388-95.

171. Schmidt-Wilcke T, Clauw DJ. Fibromyalgia: from pathophysiology to therapy. Nat Rev Rheumatol. 2011;7(9):518-27.

172. Boomershine CS, Crofford LJ. A symptom-based approach to pharmacologic management of fibromyalgia. Nature reviews Rheumatology. 2009;5(4):191-9.

173. Masseria C, Irwin R, Thomson S, Gemmill M, Mossialos E. Primary care in Europe. The London School of Economics and Political Science 2009.

174. Arguasca T, Argimon J. Country Case Study Spain: Primary care in Catalonia. Improving primary care in Europe and the US: Towards patient-centered, proactive and coordinated systems of care2008. p. 1-16.

175. Briggs AH, Claxton K, Sculpher MJ. Decision Modelling for Health Economic Evaluation: Oxford University Press; 2006.

176. Office for National Statistics (2016). UK National Life Tables, 1980-82 to 2013-15. Available from: http://www.ons.gov.uk/ons/datasets-and-tables/index.html

177. Chandran A, Schaefer C, Ryan K, Baik R, McNett M, Zlateva G. The comparative economic burden of mild, moderate, and severe fibromyalgia: results from a retrospective chart review and cross-sectional survey of working-age U.S. adults. J Manag Care Pharm. 2012;18(6):415-26.

178. Winkelmann A, Perrot S, Schaefer C, Ryan K, Chandran A, Sadosky A, et al. Impact of fibromyalgia severity on health economic costs: results from a European cross-sectional study. Appl Health Econ Health Policy. 2011;9(2):125-36.

179. Executive N. National Schedule of Reference Costs 2012-2013. In: Health Do, editor. London2013.

180. Curtis L, Burns A. Unit Costs of Health and Social Care 2016 2016. Available from: http://www.pssru.ac.uk.

181. Association BM. British National Formulary. In: Books B, editor. 69th ed. London: Royal Pharmaceutical Society of Great Britain; 2015.

182. Curtis L. Unit Costs of Health and Social Care 2014. 2014. Available from: http://www.pssru.ac.uk.

183. Curtis L. Unit Costs of Health and Social Care 2010. 2010. Available from: http://www.pssru.ac.uk.

184. Department of Health. NHS National Schedule of Reference Costs 2015-2016 2015-16. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016.

185. Wright M, Grieve R, Roberts J, Main J, Thomas H. UK Mild Hepatitis C Trial Investigators: Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess. 2006;10(21):1-113.

186. Perrot S, Schaefer C, Knight T, Hufstader M, Chandran AB, Zlateva G. Societal and individual burden of illness among fibromyalgia patients in France: association between disease severity and OMERACT core domains. BMC Musculoskelet Disord. 2012;13(22):1471-2474.

187. Schaefer C, Chandran A, Hufstader M, Baik R, McNett M, Goldenberg D, et al. The comparative burden of mild, moderate and severe fibromyalgia: results from a cross-sectional survey in the United States. Health and quality of life outcomes. 2011;9(1):1.

188. Norton G. Cost-Utility of Cognitive Behavioral Therapy for Low Back Pain From the Commercial Payer Perspective. 2015;40(10):725-33.

189. Great Britain HM. The Green Book: appraisal and evaluation in central government : Treasury guidance. London: TSO; 2003. Available from https://www.gov.uk/government/publications/the-green-book-appraisal-and-evaluation-in-central-governent

190. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. Value Health. 2012;15(6):812-20.

191. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. The British Journal of Psychiatry. 2005;187(2):106-8.

192. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. 2001;10:779-87.

193. National Institute for Health and Clinical Excellence. The guidelines manual. London; 2007.

194. O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: an introduction to statistical issues and methods. Statistical methods in medical research. 2002;11(6):455-68.

195. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

196. National Institute of Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. London: NICE; 2008. Available from http://www.med.mcgill.ca/epidemiology/courses/EPIB654/Summer2010/NICE/NICE%20Methods%20of%20Tech%20Appraisal.pdf

197. National Institute of Health and Clinical Excellence (NICE). Guide to the Methods of Technology Appraisal. London: NICE; 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword

198. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. The European Journal of Health Economics. 2010;11(4):427-34.

199. Mortimer D, Segal L. Comparing the incomparable? A systematic review of competing techniques for converting descriptive measures of health status into QALY-weights. Medical decision making. 2008;28(1):66-89.

200. Skaltsa K, Longworth L, Ivanescu C, Phung D, Holmstrom S. Mapping the FACT-P to the Preference-Based EQ-5D Questionnaire in Metastatic Castration-Resistant Prostate Cancer. Value in Health. 2014;17(2):238-44.

201. Payakachat N, Summers KH, Pleil AM, Murawski MM, Thomas J, 3rd, Jennings K, et al. Predicting EQ-5D utility scores from the 25-item National Eye Institute Vision Function Questionnaire (NEI-VFQ 25) in patients with age-related macular degeneration. Qual Life Res. 2009;18(7):801-13.

202. Chen G, Khan MA, Iezzi A, Ratcliffe J, Richardson J. Mapping between 6 Multiattribute Utility Instruments. Medical Decision Making. 2016;36(2):160-75.

203. Szende A, Oppe M, Devlin N. EQ-5D Value Sets: Inventory, Comparative Review and User Guide: Springer Netherlands; 2007. Available from http://www.springer.com/gb/book/9781402055102

204. Browne C, Brazier J, Carlton J, Alavi Y, Jofre-Bonet M. Estimating quality-adjusted life years from patient-reported visual functioning. Eye. 2012;26(10):1295-301.

205. Sullivan PW, Ghushchyan V. Mapping the EQ-5D Index from the SF-12: US General Population Preferences in a Nationally Representative Sample. Medical decision making : an international journal of the Society for Medical Decision Making. 2006;26(4):401-9.

206. Tsuchiya A, Brazier J, McColl E, Parkin D. Deriving preference-based single indices from non-preference based condition specific instruments: converting AQLQ into EQ-5D indices. HEDS discussion paper; 2002.

207. Gray AM, Rivero-Arias O, Clarke PM. Estimating the association between SF-12 responses and EQ-5D utility values by response mapping. Medical Decision Making. 2006;26(1):18-29.

208. Kennedy P. A Guide to Econometrics. 6th ed: Wiley-Blackwell; 2008.

209. Petrou S, Rivero-Arias O, Dakin H, Longworth L, Oppe M, Froud R, et al. The MAPS reporting statement for studies mapping onto generic preference-based outcome measures: explanation and elaboration. Pharmacoeconomics. 2015;33(10):993-1011.

210. Petrou S, Rivero-Arias O, Dakin H, Longworth L, Oppe M, Froud R, et al. Preferred reporting items for studies mapping onto preference-based outcome measures: The MAPS statement. Health and Quality of Life Outcomes. 2015;13(1):106.

211. Luciano JV, García-Forero C, Cerdà-Lafont M, Peñarrubia-María MT, Fernández-Vergel R, Cuesta-Vargas AI, et al. Functional Status, Quality of Life, and Costs Associated With Fibromyalgia Subgroups: A Latent Profile Analysis. The Clinical Journal of Pain. 2015;Publish Ahead of Print.

212. Longworth L, Yang Y, Young T, Hernandez Alva M, Mukuria C, Rowen D, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: systematic review, statistical modelling and survey. 2014.

213. Versteegh MM, Leunis A, Uyl-de Groot CA, Stolk EA. Condition-Specific Preference-Based Measures: Benefit or Burden? Value in Health. 2012;15(3):504-13.

214. Hawton A, Green C, Telford C, Zajicek J, Wright D. Using the Multiple Sclerosis Impact Scale to estimate health state utility values: mapping from the MSIS-29, version 2, to the EQ-5D and the SF-6D. Value Health. 2012;15(8):1084-91.

215. Joyce VR, Sun H, Barnett PG, Bansback N, Griffin SC, Bayoumi AM, et al. Mapping MOS-HIV to HUI3 and EQ-5D-3L in Patients With HIV. MDM Policy & Practice. 2017;2(2):2381468317716440.

216. Barton GR, Sach TH, Jenkinson C, Avery AJ, Doherty M, Muir KR. Do estimates of cost-utility based on the EQ-5D differ from those based on the mapping of utility scores? Health Qual Life Outcomes. 2008;6:51.

217. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.

218. Longworth L, Rowen D. Mapping to Obtain EQ-5D Utility Values for Use in NICE Health Technology Assessments. Value in Health. 2013;16(1):202-10.

219. Sculpher M, Drummond M, Buxton M. The iterative use of economic evaluation as part of the process of health technology assessment. Journal of health services research & policy. 1997;2(1):26-30.

220. The National Pain Audit (2012). Available from http://www.nationalpainaudit.org/media/files/NationalPainAudit-2012.pdf (accessed 12 April 2017).

221. The Faculty of Pain Medicine.The Faculty of Pain Medicine Workforce Analysis. Available from http://www.rcoa.ac.uk/faculty-of-pain-medicine/workforce (accessed 12 April 2017).

222. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. British journal of anaesthesia. 2013;111(1):13-8.

223. Parliamentary Business 2010 The Ageing Population. Available from http://www.parliament.uk/documents/commons/lib/research/key_issues/Key-Issues-The-ageing-population2007.pdf (accessed 12 April 2017).

224. McGhie J, Grady K. Where now for UK chronic pain management services? British journal of anaesthesia. 2016;116(2):159-62.

225. Van Koulil S, Effting M, Kraaimaat F, Van Lankveld W, Van Helmond T, Cats H, et al. Cognitive–behavioural therapies and exercise programmes for patients with fibromyalgia: state of the art and future directions. Annals of the Rheumatic Diseases. 2007;66(5):571-81.

226. Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science. J Pain. 2004;5(4):195-211.

227. van der Werf SP, de Vree B, Alberts M, van der Meer JW, Bleijenberg G. Natural course and predicting self-reported improvement in patients with chronic fatigue syndrome with a relatively short illness duration. J Psychosom Res. 2002;53(3):749-53.

228. Mood AMF, Graybill FA, Boes DC. Introduction to the theory of statistics1974.

229. Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennett CL, Cella D, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol. 2002;20.

230. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16.

231. Sellors J, Cosby R, Trim K, Kaczorowski J, Howard M, Hardcastle L, et al. Recruiting family physicians and patients for a clinical trial: lessons learned. Family practice. 2002;19(1):99-104.

232. Bell-Syer SEM, Moffett JAK. Recruiting patients to randomized trials in primary care: principles and case study. Family practice. 2000;17(2):187-91.

233. Fletcher K, Mant J, Holder R, Fitzmaurice D, Lip GYH, Hobbs FDR. An analysis of factors that predict patient consent to take part in a randomized controlled trial. Family practice. 2007;24(4):388-94.

234. Mulvenna PM, Nankivell MG, Barton R, Faivre-Finn C, Wilson P, Moore B, et al. Whole brain radiotherapy for brain metastases from non-small lung cancer: Quality of life (QoL) and overall survival (OS) results from the UK Medical Research Council QUARTZ randomised clinical trial (ISRCTN 3826061). Journal of Clinical Oncology. 2015;33(15_suppl):8005.

235. Richards DA, Hallberg IR. Complex interventions in health: an overview of research methods: Routledge; 2015.

236. Eldridge SM, Ashby D, Feder GS, Rudnicka AR, Ukoumunne OC. Lessons for cluster randomized trials in the twenty-first century: a systematic review of trials in primary care. Clin Trials. 2004;1(1):80-90.

237. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. BMJ. 2009;339.

238. Forster A, Young J, Chapman K, Nixon J, Patel A, Holloway I, et al. Cluster Randomized Controlled Trial: Clinical and Cost-Effectiveness of a System of Longer-Term Stroke Care. Stroke. 2015;46(8):2212-9.

239. Carmona-Terés V, Lumillo-Gutiérrez I, Jodar-Fernández L, Rodriguez-Blanco T, Moix-Queraltó J, Pujol-Ribera E, et al. Effectiveness and cost-effectiveness of a health coaching intervention to improve the lifestyle of patients with knee osteoarthritis: cluster randomized clinical trial. BMC Musculoskeletal Disorders. 2015;16(1):38.

240. Boyd M, Waring J, Barber N, Mehta R, Chuter A, Avery AJ, et al. Protocol for the New Medicine Service Study: a randomized controlled trial and economic

evaluation with qualitative appraisal comparing the effectiveness and cost effectiveness of the New Medicine Service in community pharmacies in England. Trials. 2013;14:411.

241. Elliott RA, Tanajewski L, Gkountouras G, Avery AJ, Barber N, Mehta R, et al. Cost Effectiveness of Support for People Starting a New Medication for a Long-Term Condition Through Community Pharmacies: An Economic Evaluation of the New Medicine Service (NMS) Compared with Normal Practice. PharmacoEconomics. 2017;35(12):1237-1255.

242. Foster NE, Healey EL, Holden MA, Nicholls E, Whitehurst DGT, Jowett S, et al. A multicentre, pragmatic, parallel group, randomised controlled trial to compare the clinical and cost-effectiveness of three physiotherapy-led exercise interventions for knee osteoarthritis in older adults: the BEEP trial protocol (ISRCTN: 93634563). BMC Musculoskeletal Disorders. 2014;15:254.

243. Avery AJ, Rodgers S, Cantrill JA, Armstrong S, Cresswell K, Eden M, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. The Lancet. 2015;379(9823):1310-19.

244. Hadi MA, Alldred DP, Closs SJ, Marczewski K, Briggs M. A mixed-methods evaluation of a nurse-pharmacist–managed pain clinic. Canadian Pharmacists Journal / Revue des Pharmaciens du Canada. 2013;146(4):197-201.

245. Wigers SHr, Stiles T, Vogel P. Effects of aerobic exercise versus stress management treatment in fibromyalgia. Scandinavian journal of rheumatology. 1996;25(2):77-86.

246. Lindh M, Lurie M, Sanne H. A randomized prospective study of vocational outcome in rehabilitation of patients with non-specific musculoskeletal pain: a multidisciplinary approach to patients identified after 90 days of sick-leave. Scandinavian journal of rehabilitation medicine. 1997;29(2):103-12.

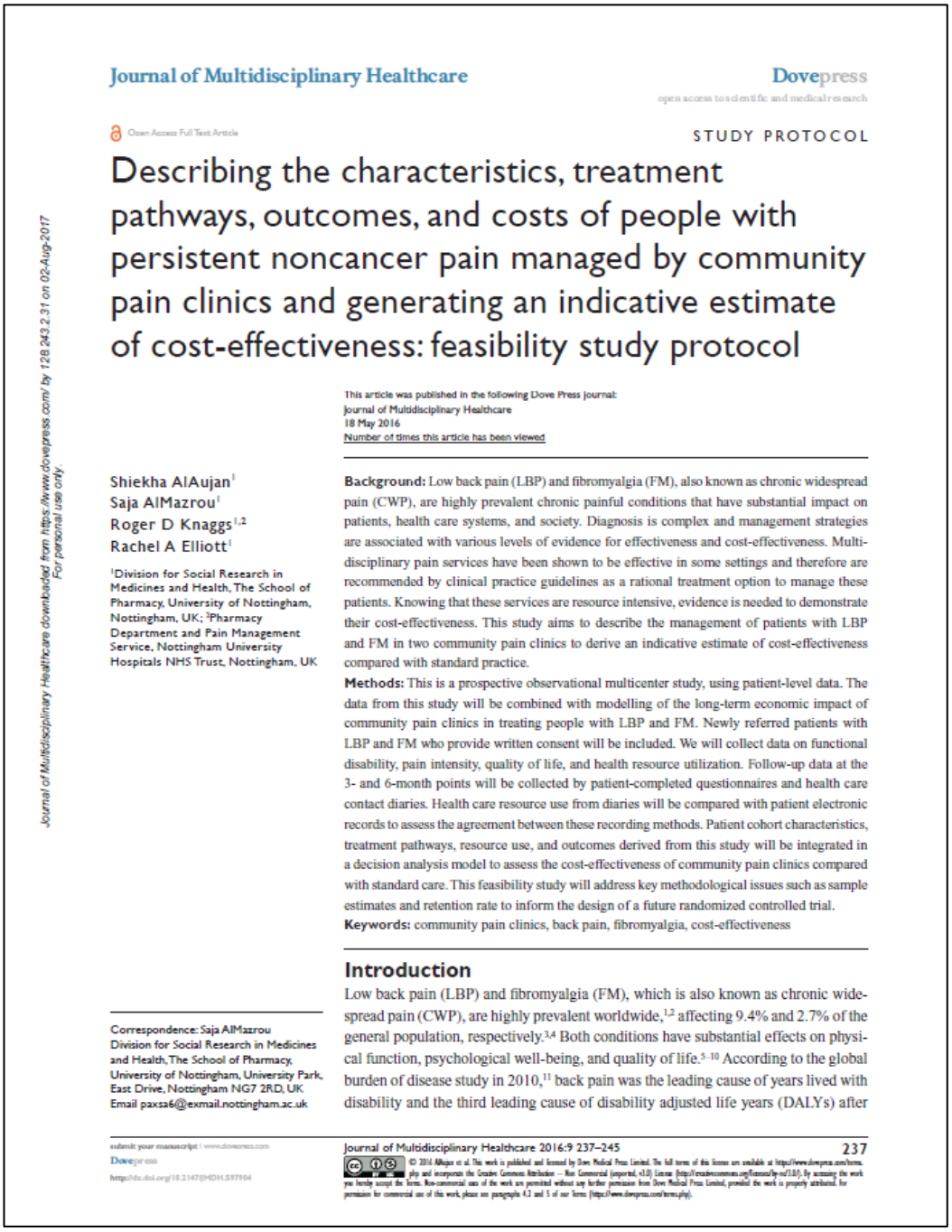
247. D'agostino RB, Belanger A, D'Agostino Jr RB. A suggestion for using powerful and informative tests of normality. The American Statistician. 1990;44(4):316-21.

248. Royston J. An extension of Shapiro and Wilk's W test for normality to large samples. Applied Statistics. 1982;31(2):115-24.

249. UCLA: Statistical Consulting Group. Regression with Stata. Available from: http://www.ats.ucla.edu/stat/stata/webbooks/reg/chapter2/statareg2.htm.

Appendices

Appendix 1. Study protocol paper



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STUDY PROTOCOL

Describing the characteristics, treatment pathways, outcomes, and costs of people with persistent noncancer pain managed by community pain clinics and generating an indicative estimate of cost-effectiveness: feasibility study protocol

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Background: Low back pain (LBP) and fibromyalgia (FM), also known as chronic widespread pain (CWP), are highly prevalent chronic painful conditions that have substantial impact on patients, health care systems, and society. Diagnosis is complex and management strategies are associated with various levels of evidence for effectiveness and cost-effectiveness. Multidisciplinary pain services have been shown to be effective in some settings and therefore are recommended by clinical practice guidelines as a rational treatment option to manage these patients. Knowing that these services are resource intensive, evidence is needed to demonstrate their cost-effectiveness. This study aims to describe the management of patients with LBP and FM in two community pain clinics to derive an indicative estimate of cost-effectiveness compared with standard practice.

Methods: This is a prospective observational multicenter study, using patient-level data. The data from this study will be combined with modelling of the long-term economic impact of community pain clinics in treating people with LBP and FM. Newly referred patients with LBP and FM who provide written consent will be included. We will collect data on functional disability, pain intensity, quality of life, and health resource utilization. Follow-up data at the 3- and 6-month points will be collected by patient-completed questionnaires and health care contact diaries. Health care resource use from diaries will be compared with patient electronic records to assess the agreement between these recording methods. Patient cohort characteristics, treatment pathways, resource use, and outcomes derived from this study will be integrated in a decision analysis model to assess the cost-effectiveness of community pain clinics compared with standard care. This feasibility study will address key methodological issues such as sample estimates and retention rate to inform the design of a future randomized controlled trial.

Keywords: community pain clinics, back pain, fibromyalgia, cost-effectiveness

Introduction

Low back pain (LBP) and fibromyalgia (FM), which is also known as chronic widespread pain (CWP), are highly prevalent worldwide,[1,2] affecting 9.4% and 2.7% of the general population, respectively.[3,4] Both conditions have substantial effects on physical function, psychological well-being, and quality of life.[5–10] According to the global burden of disease study in 2010,[11] back pain was the leading cause of years lived with disability and the third leading cause of disability adjusted life years (DALYs) after

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Study protocol paper (continued)

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ischemic heart disease and chronic obstructive pulmonary disease.

The economic burden of both conditions is also substantial. People with these conditions are regarded as great utilizers of health care resources.[12–15] Recently, it has been reported that health resource utilization such as prescriptions and visits for patients with back pain and FM were double those of the matched controls.[14,15] In the United Kingdom,[15] primary care consultations and referral to secondary care for LBP accounted for 58% and 22.3% of the total health care costs for back pain, respectively. Furthermore, indirect costs to society are significant, due to lower productivity and higher absenteeism.[16,17]

Managing these conditions is challenging due to many factors. First, the etiology is complex and not specific.[18–20] Also, they can be exacerbated by a wide range of sociodemographic and psychosocial factors such as illness behavior beliefs and distress.[18,21,22] Therefore, no single treatment is adequate to control all symptoms.

In order to manage pain within a biopsychosocial framework, which addresses pain as a dynamic interaction between physiological, social, and psychological elements, a multidisciplinary management approach is recommended by national and international guidelines.[21,23–25] Effectiveness of the multidisciplinary management approach has been widely investigated in LBP and FM.

In LBP, a systematic review of randomized controlled trials suggested that multidisciplinary pain services are more effective than standard care (SC) in reducing functional disability using the Roland Morris Disability (RMD) score (standardized mean difference [SMD]: 0.23, 95% confidence interval [CI]: 0.06–0.4) and pain intensity using visual analogue scale (VAS) (SMD: 0.21, 95% CI: 0.04–0.37).[26] In 2008, results from a systematic review indicated that multidisciplinary pain services were better than standard medical treatment in FM.[27] However, results are inconclusive due to the great variability of the interventions, outcomes, and study durations. The major limitation with these systematic reviews is that the methodological quality of most studies included was low.

Given that multidisciplinary pain services are resource intensive;[28,29] evidence is needed to demonstrate the cost-effectiveness of these services in LBP and FM. A small number of cost-effectiveness studies have been undertaken in Europe and the USA,[30–40] others are still in progress in Spain and the Netherlands.[41,42] These studies were conducted alongside clinical trials; however, they have methodological limitations in study design. Compliance to treatment was either inadequate[32,33,35,36,38–40] or not clearly reported.[30,31,37] Moreover, some aspects of treatments/sessions did not appear to be equally used by all participants.[32,34,36,38] Therefore, the effect cannot be directly attributed to multidisciplinary pain service.

In addition, threats to external validity may impede the application of the results to real practice.[43] These threats come from restrictive patient eligibility criteria such as employees,[30,33] recruiting from various practice settings, ie, primary and secondary care setting, and variability of intervention. This variability is either between intervention in terms of treatment components and health care staff or between study participants.

Among these studies, a wide range of comparators were used such as surgery[36,37] physiotherapy/exercise,[32,39,40] and cognitive behavioral therapy.[32,34,39,40] Six studies compared multidisciplinary pain service with usual care.[30,31,33,38–40] The definition of usual care varies according to the country and study context, this will also limit the applicability of results. Therefore, results about the cost-effectiveness of these services have been inconclusive because of the variety of interventions, participants, and outcome measures.

Community pain clinic in Nottingham

The project will take place in two community pain clinics (CPC) in Nottingham, UK. These two clinics are operated by the same clinic staff, therefore, the type and quality of health care provided are the same in both clinics. Patients may have consultations with members of the multidisciplinary team (including a pain consultant, a physiotherapist, a biopsychosocial practitioner, and a nurse) for supported self-care management, or community services such as physiotherapy, or more specialist secondary care services. The community pain clinic facilitates access to a wide range of diagnostic and treatment pathways such as MRI, rehabilitation programs, and minor procedures such as trigger point injections. In addition, complex surgical interventions can be offered. Further details on the community pain clinic in Nottingham can be found in the review by Hobbs and Knaggs.[44]

LBP and FM represent the majority of patients referred to the clinic, therefore these conditions will be the main focus of this study.

Before establishing the CPC, patients with LBP and FM were treated initially by their GPs. If treatment failed to improve patients' outcomes, then referrals to secondary care may have been considered. This SC pathway may lead to increased rates of development of chronic pain due to the

Study protocol paper (continued)

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delay in diagnosis and treatment and the long waiting time to be referred to secondary care.[45–47] Alongside the detrimental effects of treatment delay, there appears to be a high level of inappropriate spinal surgery unit referrals, suggesting that more targeted use of this service is needed.[48]

Anecdotally, impressions are that patients are benefiting from the CPC and if it were expanded, patients in the locality would benefit from better pain management. However, financial constraints prevent the possibility of expanding, or even continuity, of the current service. Evidence so far suggests that multidisciplinary pain clinics can be effective, although the effectiveness of the Nottingham CPC is not known. Given that it is likely that these types of services are highly costly and require integration between health care sectors, the effectiveness, patient acceptability, and cost-effectiveness of CPCs needs to be investigated.

Electronic administrative records can be used to estimate health resource use. It reduces data recording burden for patients, and generally provides more detail about types of health care contacts. However, the data can be time-consuming to access, and may only be reliable and complete for a specific sector (eg, hospital stays are not always recorded reliably in GP recording systems[49]). In addition, in the management of LBP, we envisage that people will use other treatments maybe outside the NHS, such as private osteopathy and physiotherapy. Patient diaries allow us to capture that patient cost. Therefore, in this observational study, we will use both methods to capture resource use data to allow us to assess which method is more reliable for future work in this patient group.

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 recognized that economic evaluation should be iterative, generating progressively firmer estimates of cost-effectiveness and helping to maximize the efficiency of health care research and development, while still allowing the best evidence available at any one time to support decision-making.[50] Therefore an indicative economic evaluation will be carried out to compare the cost-effectiveness of CPC and SC in managing LBP and FM using published estimates of effectiveness and cost.

The paucity of economic evaluations of multidisciplinary pain management services 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 CPC in Nottingham to inform decision-makers and commissioners about the effectiveness and cost-effectiveness of this service and, therefore, allocating resources in an efficient manner.

Specific objectives are to:

1. Describe the demographic characteristics of patients with LBP and FM and their treatment pathway in the CPC.
2. Determine clinical outcomes and health care costs of the CPC using patient reported outcome measures and routinely recorded health care resource use.
3. Assess the reconciliation between patient-reported and routinely recorded health care resource use data and derive cost estimations by combining the two methods.
4. Derive indicative estimates of cost-effectiveness of CPC compared with SC in managing LBP and FM combining data from this study with published estimates of effectiveness for multidisciplinary pain clinics and long-term costs and outcomes associated with LBP and FM.
5. Inform the design of a future cluster randomized trial to evaluate the effectiveness and cost-effectiveness of CPC.

Methods

Study design

This is a prospective observational multicenter study, using patient-level data. The data from this study will be combined with modelling of the long-term economic impact of community pain clinics in treating people with LBP and FM. The study design is summarized in Figure 1.

Study setting

The study will be conducted at the Nottinghamshire primary–secondary care interface. Newly referred patients to Nottingham West Clinical Commissioning Group and Newark and Sherwood CCGs who fit the eligibility criteria will be invited. Recruiting from two clinics will increase the number of participants, and therefore the study will be powered to detect difference in primary outcomes.

Sample size and justification

This is not an interventional study; so, a sample size is not required to derive an effect size. However, the sample obtained in this study will provide data to inform a future

Figure 1 Overall study design.

Study protocol paper (continued)

sample size calculation. The largest sample possible is also required to provide richer information about the patient cohort using CPC for LBP and FM.

Ethical approval

Ethical approval for the study has been obtained from North East York and East Midland-Nottingham 1 Research Ethics Committees (REC reference numbers 15/NE/0162 and 15/EM/0190).

Inclusion criteria

1. Adults (18 years or older), attending the pain clinic for the first time and who have LBP or FM for at least 3 months.
2. Participants will be required to have good understanding of the English language and the ability to understand study documents and provide written consent.

As this study will include patients with different disease states, the exclusion criteria for each condition is listed below:

Exclusion criteria for people with low back pain

1. Having an underlying organic pathology for low back pain such as infection or cancer.
2. Having had a spinal surgical procedure in the past 6 weeks or having to undergo surgery within 3 months.
3. Having severe psychiatric disorders such as major depression or psychosis.
4. Being pregnant or having given birth in the past 3 months.

Exclusion criteria for people with fibromyalgia

1. Not having a confirmed diagnosis of FM.
2. Having severe psychiatric disorders such as major depression or psychosis.

Outcome measures

Disease-specific outcome measures will be used for each disease group population. Roland Morris Disability Questionnaire[51] will be used to assess the functional disability for patients with LBP and to assess the functionality of patients with FM the Revised Symptoms Impact Questionnaire (SIQR)[52] will be used.

Pain intensity will be measured using the short-form Brief Pain Inventory (BPI),[53] whereas health status will be assessed by EuroQol-5 Dimension-3 level instrument (EQ-5D-3L).[54] A summary of the outcome measures recorded during the study is provided in Table 1.

Study regimen

This study will involve three main stages. For each stage, the aim, methodological features, outcome measures or data collected, and duration are described below.

Stage 1: observational study – assess the clinical outcomes and health care use in CPC

The pain clinic consultant will have the responsibility of identifying eligible patients at triage.[44] The initial patient approach will be from the pain clinic consultant, who will inform the participant of all aspects pertaining to participation in the study.

The questionnaires will be piloted using a small number of patients (approximately 5–10 patients) attending the two CPCs to examine the type, accuracy, and practicality of resource use data collection tools and outcome measure tools.[55] These patients will be included in the final analysis if no further amendments to the study design or data collection tools are made.

This pilot study will follow the same procedure of the main study in terms of identification, recruitment, and contact

Table 1 Summary of collected data

Stage	Outcome measure	Time point recorded	Method of recording
Observational study (stage 1)	Patients characteristics	Baseline	Questionnaire completed by telephone call
	Disease specific outcome measure: • Fibromyalgia: The Revised Symptoms Impact Questionnaire • Back pain: Roland Morris Disability Questionnaire	Baseline, 3 months, and 6 months	
	Pain intensity and interference: Brief Pain Inventory	Baseline, 3 months, and 6 months	
	Health status: EuroQol-5 dimension-3 level instrument	Baseline, 3 months, and 6 months	
	Health care resource use	3 and 6 months post referral	Self-completed diary
Costing method comparative study (stage 2)	Health care resource use	0–6 months inclusive	Patients' medical record

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method. The main study will follow the procedure detailed: The pain clinic consultant will identify and invite eligible patients to take part in the study and will explain the study to the eligible patient. If the patient has initially expressed interest in being involved in the study, the consultant will provide the patient with the study information pack. The patient will be asked to provide his/her contact details by clinic staff to arrange a telephone call with the researcher within 24–72 hours to allow the patient to consider participation in the study. To maximize retention of the study participants, each patient will determine the preferred time slot of the day for researcher to contact him/her.

Within 24–72 hours of the initial patient encounter, the researcher will contact the patient to confirm the consent and answer any questions related to the study. The patient will need to sign the consent form and send it back to the researcher by post.

The patient will be asked to answer questions related to his/her baseline pain, physical function, and health status. In addition, demographic data of patients will be obtained. The researcher will contact the patient by phone to collect clinical outcome data after 3 and 6 months. Patients will be encouraged to record their health resource use using diaries. These diaries will be returned by post at 3 and 6 months.

Stage 2: assess the agreement between patients' self-reported health resource use and medical records in CPC

This stage aims to assess health care utilization data collection methods, when resource use data are obtained from either medical records or patient self-report using a diary, by assessing the reconciliation between these two approaches and resulting cost estimations derived from the resource use data obtained. Health care resource use data from the previous stage, using patient-reported methods, will be compared with health care resource data elicited from medical records of CPC patients.

These data will be collected retrospectively for 6 months from the date of CPC referral. A data analyst will extract the data required. Data extracted will include medication use and primary and secondary health care service use; principally GP visits, emergency department visits, inpatient, outpatient attendances, and other community services (ie, physiotherapy). The data will be extracted from GP practices that use SystmOne[56] and EMIS[57] to record patients' data electronically.

Stage 3: indicative economic evaluation

Data collected from the study will be used to inform an indicative economic evaluation. Cost-effectiveness will be investigated by generating differences in costs and outcomes between SC and CPC. Published evidence on costs and outcomes for SC will be combined with outcomes and costs from the patient cohort in this study to generate mean incremental quality adjusted life years (QALY) and costs. The data will be gathered from participants for 6 months. The costs and benefits of CPC will be calculated over a 6-month period (short term). The long-term (5–10 years) costs and outcomes will be estimated using decision analysis modelling. This period will be sufficient to observe the effect of intervention on costs and outcomes;[58] therefore, two models will be constructed. The data sources for the two models are illustrated in Table 2.

The costs will be collected from health provider perspective. Intervention cost will be calculated using a "bottom–up" approach. Patients' visits to CPC and the types of treatments received will be gathered from the medical records. Direct medical cost such as visits to GP, nurses, other health care professionals, and hospitals will be recorded in costing diary. Direct nonmedical costs such as travel expenses will be also recorded in costing diary. These diaries will be administered twice during the study (3 months period).

Direct health care costs will be obtained from the following sources: costs of treatment interventions and investigations will be derived from NHS reference costs,[59] costs of health staff from the Personal Social Services Research Unit (PSSRU),[60] and medication costs from the British National Formulary[61] (March–September 2015). All costs will be expressed in 2015–2016 pounds sterling. The discount will be applied in the long-term model only; we will discount effects and costs at an annual rate of 3.5%. The UK Treasury recommended 3.5% discount rate for both costs and outcomes.[62] In addition, different discount rates will be tested in the sensitivity analysis.

Short term

We will conduct a short-term (6 months) cost-effectiveness decision analysis model from NHS perspective. Markov

Table 2 Data sources for economic models

Outcomes and costs	Short term	Long term
Intervention	Current observational study	Economic evaluation alongside observational longitudinal studies
Comparator	Economic evaluation alongside randomized clinical trials	

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model inputs will be based on the data derived from the current observational study and published literature. The short-term effect of SC on outcomes and cost will be obtained by conducting a systematic review of cost-effectiveness studies of multidisciplinary pain management services in LBP and FM.

Long term

The long-term benefit of multidisciplinary pain management services needs to be evaluated as these services are cost intensive. Moreover, little is known about the long-term effectiveness. Therefore, the model input will be based on data from published literature. Longitudinal observational studies which aim to evaluate the effectiveness and cost-effectiveness of multidisciplinary pain management services in LBP and FM will be used. The data source for the models is illustrated in Table 2.

Analyses

Stage 1: observational study

We will describe the study population and their outcomes using simple descriptive statistics, percentages for categorical, and mean and SD for continuous variables.

Changes within outcome measures over the duration of the study will be assessed using paired *t*-tests for continuous data and McNemar tests for dichotomous data.

Unit costs will be combined with resource-use from the two collection methods to generate two estimates of patient-level costs.

We will determine baseline factors associated with change of outcome measures or cost over the course of patient follow-up. This will be performed using multiple linear and logistic regression for continuous and binary outcome variables, respectively. *P*-values less than 0.05 will be considered statistically significant.

Stage 2: costing methods comparative study

Nonparametric bootstrapping will be used to compare arithmetic means of costs data.[63] Pairwise *t*-tests will be applied to the data generated by bootstrapping. Level of agreement between electronic and self-reported resource-use will be estimated by using the Lin concordance correlation coefficient,[64] which can be applied to nonnormally distributed data such as resource use data. The Lin coefficient value lies between 1, indicative of perfect agreement, and −1, indicative of perfect inverse agreement.

Stage 3: indicative economic evaluation

This economic study will be performed according to the intention-to-treat principles. For missing data during follow-up, we will use complete case analysis.

We will carry out incremental analysis, which is mean difference in cost between CPC and SC divided by the mean in QALY difference to generate incremental cost-effectiveness ratio (ICER). Nonparametric bootstrapping with 1,000 iterations will be used to calculate the confidence interval around the ICER and cost difference.

To assess the robustness of the results, deterministic univariate and multivariate sensitivity analyses will be performed. Probabilistic sensitivity analysis (PSA) will be undertaken for base-case scenario and univariate and multivariate analysis. Sampling incremental costs and QALY will be conducted by Monte Carlo simulation using TreeAge Pro. We will use cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) to present the results. All statistical analyses will be conducted using STATA 11.1.[65] TreeAge Pro[66] will be used to build the decision analysis model.

Discussion

The major strengths in this study design are that we will use validated gold standard measures for each of these patient outcomes to assess which best reflects the success and acceptability of the service from the patient perspective. We also need to obtain detailed information on treatment pathways. This is essential to understand the nature and variability of the complex intervention. It is also needed to allow us to estimate resource use and cost, associated with managing patients by the CPC. Treatment pathway and associated resource use data can be obtained either by accessing routine medical records, or by patient report. Neither method is without its limitations. In this study, we will use both methods to capture resource use data to allow us to assess which method is more reliable for future work in this patient group.

Moreover, the choice of study design was based on the Medical Research Council (MRC) recommendation for evaluating complex intervention. Multidisciplinary pain clinics such as the Nottingham CPC are considered as "complex" interventions. This complexity is derived by the number of interacting components within the clinic and variety of intended outcomes. There are known difficulties and methodological challenges in evaluating complex interventions. The MRC published a framework which recommends evaluating the intervention through observational and developmental work, followed by an exploratory trial before conducting

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the definitive evaluation. This is required to identify key uncertainties in the design and assessment of the intervention and its evaluation.[67]

Recruitment and retention rates are major limitations on any prospective study design. In this study, several data collection methods were considered, such as postal questionnaires, face-to-face interviews, and phone calls. However, there are some practical difficulties in using interviews, as patients may be referred to other health care specialists outside the clinic during the study period. For postal questionnaires, there is a risk of low response rate. Given that the study period is relatively short (6 months), telephone calls were chosen for data collection over other methods to maximize the response rate and to facilitate patient tracking. In addition, each patient will determine the preferred time slot of the day for researcher to contact him/her. If the patients did not respond to the first phone call, the researcher will contact the patient twice within 1 hour. The total number of calls will be three times, each is 20 minutes apart. Another attempt will be made on the following day in case of no response. Furthermore, the patient will be approached by letter to re-establish the contact. Participants who do not respond to phone calls after these attempts will be presumed to have withdrawn from the study and no further contact will be made.

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All patient-related paperwork, which include questionnaires, diaries, patient information sheet, and the consent form have been reviewed by Antony Chuter. Mr Chuter has significant experience in providing the patient perspective to health services research projects; he was the PPI coinvestigator for an evaluation of the New Medicine Service Project and worked with the Expert Patient Program, Royal College of General Practitioners, and currently he is Chair of the Patient Liaison Committee (British Pain Society) and Chair of Pain UK.

Disclosure

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References

1. Kohlmann T. [Musculoskeletal pain in the population]. *Schmerz*. 2003;17(6):405–411. German
2. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ*. 2003;81(9):646–656.
3. Hoy D, March L, Brooks P, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73(6):968–974.
4. Queiroz LP. Worldwide epidemiology of fibromyalgia. *Curr Pain Headache Rep*. 2013;17(8):356.
5. Yilmaz F, Sahin F, Ergoz E, et al. Quality of life assessments with SF-36 in different musculoskeletal diseases. *Clin Rheumatol*. 2008;27(3):327–332.
6. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. *Health Qual Life Outcomes*. 2008;6(8):1477–7525.
7. Birtane M, Uzunca K, Tastekin N, Tuna H. The evaluation of quality of life in fibromyalgia syndrome: a comparison with rheumatoid arthritis by using SF-36 Health Survey. *Clin Rheumatol*. 2007;26(5):679–684.
8. Hoffman DL, Dukes EM. The health status burden of people with fibromyalgia: a review of studies that assessed health status with the SF-36 or the SF-12. *Int J Clin Pract*. 2008;62(1):115–126.
9. Buchbinder R, Blyth FM, March LM, Brooks P, Woolf AD, Hoy DG. Placing the global burden of low back pain in context. *Best Pract Res Clin Rheumatol*. 2013;27(5):575–589.
10. Froud R, Patterson S, Eldridge S, et al. A systematic review and meta-synthesis of the impact of low back pain on people's lives. *BMC Musculoskelet Disord*. 2014;15:50.
11. Murray CJL, Lopez AD. Measuring the global burden of disease. *N Engl J Med*. 2013;369(5):448–457.
12. Wolfe F, Anderson J, Harkness D, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. *Arthritis Rheum*. 1997;40(9):1560–1570.
13. Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Claxton AJ. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. *J Rheumatol*. 2003;30(6):1318–1325.
14. Hughes G, Martinez C, Myon E, Taieb C, Wessely S. The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice. *Arthritis Rheum*. 2006;54(1):177–183.
15. Hong J, Reed C, Novick D, Happich M. Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. *Spine*. 2013;38(1):75–82.
16. Knight T, Schaefer C, Chandran A, Zlateva G, Winkelmann A, Perrot S. Health-resource use and costs associated with fibromyalgia in France, Germany, and the United States. *Clinicoecon Outcomes Res*. 2013;5:171–180.
17. Ricci JA, Stewart WF, Chee E, Leotta C, Foley K, Hochberg MC. Back pain exacerbations and lost productive time costs in United States workers. *Spine*. 1976;31(26):3052–3060.
18. Fourney DR, Andersson G, Arnold PM, et al. Chronic low back pain: a heterogeneous condition with challenges for an evidence-based approach. *Spine*. 2011;36(21 Suppl):S1–S9.
19. Russell IJ, Larson AA. Neurophysiopathogenesis of fibromyalgia syndrome: a unified hypothesis. *Rheum Dis Clinic North Am*. 2009;35(2):421–435.
20. Clauw DJ, Arnold LM, McCarberg BH. The science of fibromyalgia. *Mayo Clin Proc*. 2011;86(9):907–911.
21. Waddell G. *The Back Pain Revolution*. Edinburgh, Scotland: Churchill Livingstone; 2004.
22. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990;33(2):160–172.
23. Savigny P, Kuntze S, Watson P, et al. *Low Back Pain: Early Management of Persistent Non-Specific Low Back Pain*. London, UK: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2009.
24. Carville SF, Arendt-Nielsen S, Bliddal H, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis*. 2008;67(4):536–541.
25. Keel P. Pain management strategies and team approach. *Baillieres Best Pract Res Clin Rheumatol*. 1999;13(3):493–506.

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26. Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. *Cochrane Database Syst Rev*. 2014;9:CD000963.
27. Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. *Rheumatology (Oxford)*. 2008;47(5):670–678.
28. Gatchel RJ, Okifuji A. Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. *J Pain*. 2006;7(11):779–793.
29. Robinson RL, Jones ML. In search of pharmacoeconomic evaluations for fibromyalgia treatments: a review. *Expert Opin Pharmacother*. 2006;7(8):1027–1039.
30. Skouen JS, Grasdal AL, Haldorsen EM, Ursin H. Relative cost-effectiveness of extensive and light multidisciplinary treatment programs versus treatment as usual for patients with chronic low back pain on long-term sick leave: randomized controlled study. *Spine*. 2002;27(9):901–909; discussion 909–910.
31. Luciano JV, Sabes-Figuera R, Cardenosa E, et al. Cost-utility of a psychoeducational intervention in fibromyalgia patients compared with usual care: an economic evaluation alongside a 12-month randomized controlled trial. *Clin J Pain*. 2013;29(8):702–711.
32. Smeets RJ, Severens JL, Beelen S, Vlaeyen JW, Knottnerus JA. More is not always better: cost-effectiveness analysis of combined, single behavioral and single physical rehabilitation programs for chronic low back pain. *Eur J Pain*. 2009;13(1):71–81.
33. Lambeek LC, Bosmans JE, Van Royen BJ, Van Tulder MW, Van Mechelen W, Anema JR. Effect of integrated care for sick listed patients with chronic low back pain: economic evaluation alongside a randomised controlled trial. *BMJ*. 2010;341:c6414.
34. Goossens ME, Rutten-van Molken MP, Leidl RM, Bos SG, Vlaeyen JW, Teeken-Gruben NJ. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. II. Economic evaluation. *J Rheumatol*. 1996;23(7):1246–1254.
35. Gusi N, Tomas-Carus P. Cost-utility of an 8-month aquatic training for women with fibromyalgia: a randomized controlled trial. *Arthritis Res Ther*. 2008;10(1):R24.
36. Rivero-Arias O, Campbell H, Gray A, Fairbank J, Frost H, Wilson-MacDonald J. Surgical stabilisation of the spine compared with a programme of intensive rehabilitation for the management of patients with chronic low back pain: cost utility analysis based on a randomised controlled trial. *BMJ*. 2005;330(7502):1239.
37. Johnsen LG, Hellum C, Storheim K, et al. Cost-effectiveness of total disc replacement versus multidisciplinary rehabilitation in patients with chronic low back pain: a Norwegian multicenter RCT. *Spine*. 2014;39(1):23–32.
38. Zijlstra TR, Braakman-Jansen LM, Taal E, Rasker JJ, van de Laar MA. Cost-effectiveness of Spa treatment for fibromyalgia: general health improvement is not for free. *Rheumatology*. 2007;46(9):1454–1459.
39. McBeth J, Prescott G, Scotland G, et al. Cognitive behavior therapy, exercise, or both for treating chronic widespread pain. *Arch Intern Med*. 2012;172(1):48–57.
40. Beasley M, Prescott GJ, Scotland G, et al. Patient-reported improvements in health are maintained 2 years after completing a short course of cognitive behaviour therapy, exercise or both treatments for chronic widespread pain: long-term results from the MUSICIAN randomised controlled trial. *RMD Open*. 2015;1(1):e000026.
41. Berenguera A, Pujol-Ribera E, Rodriguez-Blanco T, et al. Study protocol of cost-effectiveness and cost-utility of a biopsychosocial multidisciplinary intervention in the evolution of non-specific sub-acute low back pain in the working population: cluster randomised trial. *BMC Musculoskelet Disord*. 2011;12:194.
42. Lambeek LC, Anema JR, van Royen BJ, et al. Multidisciplinary outpatient care program for patients with chronic low back pain: design of a randomized controlled trial and cost-effectiveness study. *BMC Public Health*. 2007;7:254.
43. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value Health*. 2005;8(5):521–533.
44. Hobbs G, Knaggs R. Commissioning for pain management services. *Br J Healthc Manag*. 2011;17(7):302–306.
45. Melloh M, Elfering A, Kaser A, et al. What is the best time point to identify patients at risk of developing persistent low back pain? *J Back Musculoskelet Rehabil*. 2015;28(2):267–276.
46. Melloh M, Elfering A, Stanton TR, et al. Low back pain risk factors associated with persistence, recurrence and delayed presentation. *J Back Musculoskelet Rehabil*. 2014;27(3):281–289.
47. Choy E, Perrot S, Leon T, et al. A patient survey of the impact of fibromyalgia and the journey to diagnosis. *BMC Health Serv Res*. 2010;10:102.
48. Department of Health. The Musculoskeletal Services Framework. 2006. Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4138413. Accessed August 18, 2015.
49. Byford S, Leese M, Knapp M, et al. Comparison of alternative methods of collection of service use data for the economic evaluation health care interventions. *Health Econ*. 2007;16(5):531–536.
50. Sculpher M, Drummond M, Buxton M. The iterative use of economic evaluation as part of the process of health technology assessment. *J Health Serv Res*. 1997;2(1):26–30.
51. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine*. 1983;8(2):141–144.
52. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. *Arthritis Res Ther*. 2009;11(4):R120.
53. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23(2):129–138.
54. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199–208.
55. Drummond M, Coyle D. The role of pilot studies in the economic evaluation of health technologies. *Int J Technol Assess Health Care*. 1998;14(3):405–418.
56. The Phoenix Partnership (TPP). SystmOne. 2015. Available from: http://www.tpp-uk.com/products/systmone. Accessed July 30, 2015.
57. EMIS Health. EMIS. 2015. Available from: https://www.emishealth.com/. Accessed July 30, 2015.
58. Comans T, Raymer M, O'Leary S, Smith D, Scuffham P. Cost-effectiveness of a physiotherapist-led service for orthopaedic outpatients. *J Health Serv Res Policy*. 2014;19(4):216–223.
59. Department of Health. NHS National Schedule of Reference Costs 2012–2013. 2013. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013. Accessed August 18, 2015.
60. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care. 2015. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/. Accessed July 30, 2015.
61. Joint Formulary Committee. *British National Formulary*. 69th ed. London, UK: BMJ Group and Pharmaceutical Press; 2015.
62. Her Majesty's Treasury. The Green Book: Appraisal and Evaluation in Central Government: Treasury Guidance Great Britain. London, UK: TSO; 2003.
63. Briggs A, Gray A. The distribution of health care costs and their statistical analysis for economic evaluation. *J Health Serv Res Policy*. 1998;3(4):233–245.
64. Lin LI. A concordance correlation coefficient to evaluate reproducibility. *Biometrics*. 1989;45(1):255–268.
65. StataCorp LP. *Stata Statistical Software: Release 11.1* [computer program]. College Station, TX: StataCorp LP; 2009.
66. TreeAge Software, Inc. *TreeAge Pro 2015: Release 1.0* [computer program]. Williamstown, MA: TreeAge Software, Inc.; 2015.
67. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337:a1655.

Appendix 2. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia (1)*

History of widespread pain

Definition: Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

Pain in ≥11 of 18 tender point sites on digital palpation

Definition: Pain, on digital palpation, must be present in at least 11 of the following 18 tender point sites:

Occiput:	Bilateral, at the suboccipital muscle insertions
Lower cervical:	Bilateral, at the anterior aspects of the intertransverse spaces at C5–C7
Trapezius:	Bilateral, at the midpoint of the upper border
Supraspinatus:	Bilateral, at the origins, above the scapula spine near the medial border
Second rib:	Bilateral, at the second costochondral junctions, just lateral to the junctions on the upper surfaces
Lateral epicondyle:	Bilateral, 2 cm distal to the epicondyle
Gluteal:	Bilateral, in the upper outer quadrants of the buttocks in the anterior fold of the muscle
Greater trochanter:	Bilateral, posterior to the trochanteric prominence
Knee:	Bilateral, at the medial fat pad proximal to the joint line

Digital palpation should be performed with an approximate force of 4 kg. For a tender point to be considered "positive," the subject must state that the palpation was painful. "Tender" is not to be considered "painful."

* For classification purposes, a patient will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

Appendix 3. The Widespread Pain Index and the Symptoms severity items in the 2010, 2011, and 2016 ACR criteria (52)

1) WPI areas (areas: 0-19): note the number areas in which the patient has had pain over the last week. Score will be between 0 and 19.

Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left	Upper back
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right	Lower back
Upper arm, left	Upper leg, left	Chest	Neck
Upper arm, right	Upper leg, right	Abdomen	
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		

2) SS scale score (score: 0-12): The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general.

   a) For the each of the 3 symptoms below, indicate the level of severity over the past week using the following scale:

0 no problem
1 slight or mild problems, generally mild or intermittent
2 moderate, considerable problems, often present and/or at a moderate level
3 severe: pervasive, continuous, life-disturbing problems

- Fatigue
- Waking unrefreshed
- Cognitive symptoms

   b) Considering somatic symptoms in general, indicate whether the patient has:*

0 no symptoms
1 few symptoms
2 a moderate number of symptoms
3 a great deal of symptoms

*Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhoea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms

Appendix 4. Classification scheme for bias assessment according to The Cochrane Review Group (122)

Bias domain	Source of bias	Review authors' judgment	Support for a judgment of "Yes"
Selection bias	Method of randomisation	Was the method of randomisation adequate?	The investigators describe a random component in the sequence generation process such as: coin toss, rolling a dice, computer-generated random sequence, pre-ordered sealed envelopes, telephone call to a central office, and pre-ordered list of treatment assignments.
	Allocation concealment	Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.
	Prognostic indicators	Were the groups similar at baseline Regarding the most important prognostic Indicators?	In order to receive a "yes", groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).
Performance bias	Blinding of patients*	Was the patient blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was Tested among the patients and it was successful.
	Blinding of care provider	Was the care provider blinded to the Intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.
	Interventions provided to all groups	Were co-interventions avoided or similar	This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.
	Acceptable compliance	Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore it is necessary to assess how many sessions each patient attended.

classification scheme for bias assessment according to The Cochrane Review Group (continued)

Detection bias	Blinding of outcome assessor	Was the outcome assessor blinded to the intervention?	This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is Adequate for outcome assessors if participant blinding is scored "yes".
	Timing of outcome assessment	Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.
Attrition bias	Drop-out rate	Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored.
	Participants analysis group	Were all randomised participants analysed in the group to which they were allocated?	All randomised patients are reported/analysed in the group they were allocated to by randomisation for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions.
Reporting bias	Selective reporting	Are reports of the study free of suggestion Of selective outcome reporting?	In order to receive a "yes", the review author determines if all the results from all pre-specified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.

Appendix 5. CHEERS checklist - Items to include when reporting economic evaluations of health interventions (123)

Section/item	Item no.	Recommendation
Title	1	Identify the study as an economic evaluation, or use more specific terms such as ‘‘cost-effectiveness analysis’’ and describe the interventions compared.
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analysis), and conclusions.
Introduction		
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.
Target population	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.
Methods		
Setting	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.
Time horizon	8	State the time horizon and say why appropriate.
Discount rate	9	Report the choice of discount rate and say why appropriate.
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.
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
	11b	Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data
Preference based outcomes	12	Describe the population and methods used to elicit preferences for outcomes.
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.
	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.
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
Choice of model	15	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytic model.
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.
Results		
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

CHEERS criteria (continued)

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.
Characterising uncertainty	20a	Single study–based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, 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.
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 in effects that are not reducible by more information.
Discussion		
Study findings	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
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.
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.

Appendix 6. Search strategies and results

		Terms	Records
Disease	1	Fibromyalgia	39587
	2	fibromyalgia syndrome	5735
	3	chronic widespread pain	2448
	4	fibromyal*	39717
	5	1 or 2 or 3 or 4	40370
Pain management services	6	multidisciplinar$	262597
	7	interdisciplinar$	156073
	8	multiprofessional$.	6079
	9	multimodal$.	165862
	10	patient care team	56115
	11	exp patient care management/	1117439
	12	patient education	217883
	13	social support	239651
	14	social environment	92740
	15	pain clinics	4212
	16	pain clinic	9811
	17	pain center$	3746
	18	pain service$	3926
	19	pain relief unit$	184
	20	pain centre$	915
	21	social work	84232
	22	occupational therapy	57835
	23	rehabilitation, vocational.	8990
	24	rehabilitation centres	12144
	25	rehabilitation clinic$	5667
	26	rehabilitation	573413
	27	exp treatment outcome/	1783051
	28	exp behavior therapy/	110392
	29	Or/ 6-28	4330508

Search strategies, dates and results (continued)

Economic evaluation	30	Health economic	17483
	31	Economic evaluation	30973
	32	Health care costs	85319
	33	Pharmacoeconomic.	12533
	34	Econom$	1239608
	35	Cost$	2139813
	36	Price$	209971
	37	Expenditure Not energy	57727
	38	Value	3432218
	39	Money	162613
	40	Budget	108980
	41	cost savings	61234
	42	cost-effective*	446545
	43	cost-benefit	162302
	44	cost-utility	17117
	45	economic*	1158451
	46	cost analysis	81135
	47	health care costs	85319
	48	Or/ 30-47	6037070
Combining and applying limits	49	5 and 29 and 42	3592
	50	limit 49 to English language	3528
	51	limit 50 to full text	651
	52	remove duplicates from 51	620

Appendix 7. Patient information sheet

The University of Nottingham
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Participant Information Sheet
(Draft Version 2.0 / Final version 1.0: 25\3\2015)

Describing the characteristics, treatment pathways, outcomes and costs of people with fibromyalgia or chronic widespread pain managed by community pain clinics, and generating an indicative estimate of cost-effectiveness

Name of Researcher(s): Shiekha Alaujan

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 Hospitals and improving medication use. Knowing that these services are costly to the National Health services (NHS), evidence is needed to demonstrate their cost effectiveness.

This study aims to describe patients' characteristics, treatment pathways, clinical outcomes and costs of fibromyalgia or chronic widespread 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 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 envelops 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. Furthermore, a data analyst will extract the same data from your medical record in order to compare between these two methods.

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. 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 (Shiekha Alaujan) 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 may 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 this study i.e. information reported by you and extracted data from your medical record 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.

The primary investigator will be the only person to have access to your personal information. All information which is collected about you during the course of the research will be kept strictly confidential, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the clinic will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.
The data collected will be kept in the university 7 years after the completion of the study. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data

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 medication or 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 University of Nottingham.

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

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PALS (Patient Advice and Liaison Service)

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Highbury Hospital
NG6 9DR
Email: PALS@nottshc.nhs.uk

Appendix 8. Consent form

The University of Nottingham

UNITED KINGDOM • CHINA • MALAYSIA

(Form to be printed on local headed paper)

CONSENT FORM
(Draft Version 2.0 / Final version 1.0: 25\3\2015)

Describing the characteristics, treatment pathways, outcomes and costs of people with fibromyalgia or chronic widespread 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: Shiekha Alaujan

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 1.0 dated 25\3\2015 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 medical notes and 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

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

Appendix 9. Patients' quationnaires

The University of Nottingham

Describing the characteristics, treatment pathways, outcomes and costs of people with fibromyalgia (FM) or chronic widespread pain (CWP) managed by community pain clinics, and generating an indicative estimate of cost-effectiveness

We are interested in understanding the impact of widespread pain/fibromyalgia on your daily living.

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 end of this questionnaire.

The questionnaire will take **10minutes** to complete.

1

Describing the management of fibromyalgia by community pain clinic. Questionnaires Draft 1.2 Final Version 1.0 20\3\2015

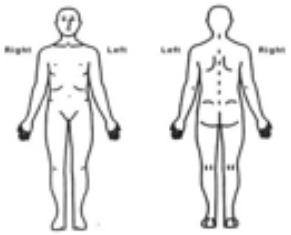
Patients' quationnaires (continued)

Pain assessment

Q1. 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**

Q2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



Q3. Please rate your pain by circling the one 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**

Q4. Please rate your pain by circling the one 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**

Q5. Please rate your pain by circling the one 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**

Q6. Please rate your pain by circling the one 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**

Patients' quationnaires (continued)

Q7. What treatments or medications are you receiving for your pain?

Q8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one 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**

Q9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										**Completely interferes**

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										**Completely interferes**

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										**Completely interferes**

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

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										**Completely interferes**

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										**Completely Interferes**

Patients' quationnaires (continued)

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Symptoms Impact Questionnaire

Q10. For each of the following 9 questions tick the box that best indicates how much difficulty you have experienced in doing the following activities during the past 7 days. If you did not perform a particular activity in the last 7 days, rate the difficulty for the last time you performed the activity. If you can't perform an activity, check the last box.

Brush or comb your hair	No difficulty □ □ □ □ □ □ □ □ □ □ □ Very difficult
Walk continuously for 20 minutes	No difficulty □ □ □ □ □ □ □ □ □ □ □ Very difficult
Prepare a homemade meal	No difficulty □ □ □ □ □ □ □ □ □ □ □ Very difficult
Vacuum, scrub or sweep floors	No difficulty □ □ □ □ □ □ □ □ □ □ □ Very difficult
Lift and carry a bag full of groceries	No difficulty □ □ □ □ □ □ □ □ □ □ □ Very difficult
Climb one flight of stairs	No difficulty □ □ □ □ □ □ □ □ □ □ □ Very difficult
Change bed sheets	No difficulty □ □ □ □ □ □ □ □ □ □ □ Very difficult
Sit in a chair for 45 minutes	No difficulty □ □ □ □ □ □ □ □ □ □ □ Very difficult
Go shopping for groceries	No difficulty □ □ □ □ □ □ □ □ □ □ □ Very difficult

Patients' quationnaires (continued)

Q11. For each of these 2 questions, tick the one box that best describes the overall impact of any medical problems over the past 7 days:

My medical problems prevented me accomplishing goals for the week	Never □ □ □ □ □ □ □ □ □ □ □ Always
I was completely overwhelmed by my medical problems	Never □ □ □ □ □ □ □ □ □ □ □ Always

Q12. For each of the following 10 questions, select the one box that best indicates the intensity, over the past 7 days, of the following common symptoms.

Please rate your level of pain	No pain	□ □ □ □ □ □ □ □ □ □ □	Unbearable pain
Please rate your level of energy	Lots of energy	□ □ □ □ □ □ □ □ □ □ □	No energy
Please rate your level of stiffness	No stiffness	□ □ □ □ □ □ □ □ □ □ □	Severe stiffness
Please rate the quality of your sleep	Awoke well rested	□ □ □ □ □ □ □ □ □ □ □	Awoke very tired
Please rate your level of depression	No depression	□ □ □ □ □ □ □ □ □ □ □	Very depressed
Please rate your level of memory problems	Good memory	□ □ □ □ □ □ □ □ □ □ □	Very poor memory
Please rate your level of anxiety	Not anxious	□ □ □ □ □ □ □ □ □ □ □	Very anxious
Please rate your level of tenderness to touch	No tenderness	□ □ □ □ □ □ □ □ □ □ □	Very tender
Please rate your level of balance problems	No imbalance	□ □ □ □ □ □ □ □ □ □ □	Severe imbalance
Please rate your level of sensitivity to loud noises, bright lights, odors and cold	No sensitivity	□ □ □ □ □ □ □ □ □ □ □	Extreme sensitivity

Patients' quationnaires (continued)

Your Health Today

Q.13 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

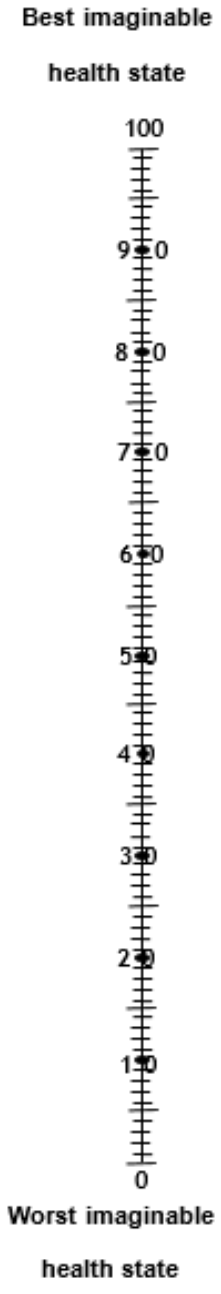
□ I am extremely anxious or depressed

Patients' quationnaires (continued)

Q14. 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.

Your own health state today



Patient identifier:

Some questions about you

Q15. How long have you been troubled by fibromyalgia/ chronic widespread pain? This means when your condition first ever started.

_____weeks _____ months _____ years

Q16. Do you take (prescribed) medicines for your fibromyalgia/ chronic widespread pain?

o No

o Yes (please specify number of medicines below)

Q17. Do you take (over the counter) medicines for your fibromyalgia/ chronic widespread pain?

o No

o Yes (please specify number of medicines below)

Q18. Do you have any other medical conditions?

o No

o Yes (please list your other medical conditions below)

Q19. If yes, do you take medicines for these conditions?

o No

o Yes (please specify number of medicines below)

Patients' quationnaires (continued)

Patient identifier:

Q20. Please tick the one option below which describe your marital status

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

Q21. 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) _____

Q22.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) _____

Q23.Have you been unable to carry out the above activities during last 6 months due to fibromyalgia or chronic widespread pain?

o Yes o No

If yes, for how long

_____weeks _____ months _____ years

Patients' quationnaires (continued)

Q24. Choose one section from A to E, then tick one box to best describe your ethnic group or background.

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

Q25. Are you

o Male o Female

Q26. How old are you? (Please give your answers in years)

Patients' quationnaires (continued)

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!

Investigator: Shiekha AlAujan
Phone: (44) (0) 7478712279
Fax: (44) (0) 115 846 6249
Email: paxsa5@exmail.nottingham.ac.uk

Academic supervisors: Prof. Rachel Elliott (Principal supervisor)
Tel: (44) (0) 115 8468596
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Dr Roger Knaggs (co-supervisor)
Tel: (44) (0) 115 84 66382
Fax: (44) (0) 115 846 6249
Email: roger.knaggs@nottingham.ac.uk

Appendix 10. Ethical approval from NRES Committee North East – York (REC reference numbers 15/NE/0162)

NHS
Health Research Authority
NRES Committee North East - York
Jarrow Business Centre
Viking Business Park
Rolling Mill Road
Jarrow, Tyne & Wear
NE32 3DT

Telephone: 0191 4283545

23 April 2015

Professor Rachel Elliott
Division for Social Research in Medicines and Health
School of Pharmacy, University of Nottingham
East Drive,
University Park,
Nottingham
NG7 2RD

Dear Professor Elliott

Study title:	**Describing the characteristics, treatment pathways, outcomes and costs of people with fibromyalgia or chronic widespread pain managed by community pain clinics in Nottingham, and generating an indicative estimate of cost-effectiveness**
REC reference:	**15/NE/0162**
Protocol number:	**15028**
IRAS project ID:	**166563**

Thank you for your e-mail correspondence which was received on 23rd April 2015, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

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 Hayley Henderson, nrescommittee.northeast-york@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 approval from NRES (continued)

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

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

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with

Appendix 11. Ethical approval from Research and Development Management Nottinghamshire Healthcare NHS foundation Trust

positive

Nottinghamshire Healthcare NHS
NHS Foundation Trust

Research and Development
Nottinghamshire Healthcare NHS Foundation Trust
Duncan Macmillan House
Porchester Road
Mapperley
Nottingham
NG3 6AA
E-mail: shirley.mitchell@nottshc.nhs.uk

Our Ref: AlAujan/NCoCCG/290515

Shiekha AlAujan, PhD student
School of Pharmacy
University of Nottingham
University Park
Nottingham
NG7 2RD

Date of letter: 29/05/2015

Dear Shiekha,

Study Title: Describing the management of Fibromyalgia in community pain clinic – V1
Principal Investigator: Shiekha AlAujan
Chief Investigator: Prof Rachel Elliott
REC ID: 15/NE/0162
CCG Information: Community Pain Clinics (CPCs) within Nottingham West CCG and Newark, and Sherwood CCG.
Sponsor: University of Nottingham

Thank you for submitting your application for the above study. Your application has been reviewed by Nottinghamshire Healthcare NHS Foundation Trust Research Support Service. We provide a research governance function for GP practices in Nottingham City and Nottinghamshire County. We provide assurance that research studies meet nationally agreed research governance criteria to assist GP practices in deciding whether to take part in a research study.

I am pleased to confirm that this application has satisfied the governance criteria for Participant Identification Centres[1]

This assurance is issued on the basis that the study is conducted in accordance with the following version of the protocol and supporting documents submitted with your application (see below).

Document	Version Number	Date
Consent Form	1.0	25/03/2015
Diary	1.0	25/03/2015
Participant Information Sheet	1.0	25/03/2015
Participant Information Sheet Pilot	1.0	25/03/2015

[1]Where potential participants will be identified through NHS organisations other than research sites themselves; these organisations are termed 'Participant Identification Centres' (PIC) IRAS Question Specific Guidance – Part C version 2.2 dated April 2009

Appendix 12. Good clinical practice certificate

NHS
National Institute for Health Research
Clinical Research Network

Certificate of Completion

Shiekha AlAujan

has completed

Introduction to Good Clinical Practice (GCP) e-learning course

A practical guide to ethical and scientific quality standards in clinical research

on 3 April 2015

Modules completed

Introduction to Research in the NHS
Good Clinical Practice and Standards in Research
Study Set-up and Responsibilities
The Process of Informed Consent
Data Collection and Documentation
Safety Reporting
Summary

Informed Consent in Paediatric Research

National Institute for Health Research
Clinical Research Network

Appendix 13. Ethical approval for the amendments from NRES Committee North East – York (REC reference numbers 15/NE/0162)

NHS
Health Research Authority
North East - York Research Ethics Committee
Jarrow Business Centre
Viking Business Park
Rolling Mill Road
Jarrow, Tyne & Wear
NE32 3DT

Tel: 0191 428 3476

30 October 2015

Professor Rachel Elliott
Division for Social Research in Medicines and Health
School of Pharmacy
University of Nottingham
East Drive
University Park
Nottingham
NG7 2RD

Dear Professor Elliott

Study title:	**Describing the characteristics, treatment pathways, outcomes and costs of people with fibromyalgia or chronic widespread pain managed by community pain clinics in Nottingham, and generating an indicative estimate of cost-effectiveness**
REC reference:	**15/NE/0162**
Protocol number:	**15028**
Amendment number:	**Substantial Amendment 1, 15/10/2015**
Amendment date:	**16 October 2015**
IRAS project ID:	**166563**

The above amendment was reviewed by the Sub-Committee in correspondence.

Summary of Opinion

Submission of this amendment was to offer participants shop vouchers for participating in the study. It was also to change the way in which participants sign the consent form and to extend the study period.

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.

The Sub-Committee reviewed the substantial amendment and requested consent to be confirmed at the same time when the participant was at the clinic rather than later when the participant was telephoned. The participant information sheet and the protocol were required to be submitted.

The applicant responded with updated documentation.

Appendix 14. Ethical approval for the amendments from Research and Development Management Nottinghamshire Healthcare NHS foundation Trust

AlAujan Shiekha

From: Mitchell Shirley - Head of Research and Innovation <Shirley.Mitchell@nottshc.nhs.uk>
Sent: 04 November 2015 15:37
To: AlAujan Shiekha
Cc: sponsor@nottingham.ac.uk
Subject: Shiekha Alaujan/Substantial Amendment 1 : Continuing NHS Assurance for Community Pain Clinics (CPCs) within Nottingham West CCG and Newark, and Sherwood CCG.

Dear Shiekha

Thank you for sending me information on the substantial amendment where the protocol and participant information sheet were updated:

- Study Protocol version 4 28/10/15
- Participant Information Sheet version 4 28/10/15

Please accept this email as continuing NHS assurance for CPCs within Nottingham West and Newark & Sherwood CCGs, however could you please let me know what date is for the study extension so we can update our database.

Thank you in advance
Regards

Shirley

Shirley Mitchell
Head of Research and Innovation
Nottinghamshire Healthcare NHS Foundation Trust
Duncan MacMillan House
Porchester Road
Mapperley
Nottingham
NG3 6AA
Mobile: 07920 454530
Telephone: 0115 9691300 ext. 11903
Email: shirley.mitchell@nottshc.nhs.uk

From: Shiekha Alaujan [mailto:paxsa5@nottingham.ac.uk]
Sent: 02 November 2015 14:42
To: Mitchell Shirley - Head of Research and Innovation; Whyatt Kayley - Research and Development Support Officer
Cc: Bb-Sponsor; Roger Knaggs (Roger.Knaggs@nottingham.ac.uk); Rachel Elliott
Subject: FW: 15/NE/0162 Query for amendments for ethics application

Dear all

Some amendments have been done on the project entitled: Describing the characteristics, treatment pathways, outcomes and costs of people with fibromyalgia or chronic widespread pain managed by community pain clinics in Nottingham, and generating an indicative estimate of cost-effectiveness. REC reference 15/NE/0162.

In the attachment you can find the REC approval for the amendments and the amended protocol and patients information sheet. If there any other documents you need it please let me know.

1

Appendix 15. Health care services cost*

Healthcare service	Unit cost (£), range if available	Comments
General Practitioner visits	36	(section 10.3b), PSSRU 2016 (180) (contact for 9.2 minutes from PSSRU 2016 (180))
Physiotherapist specific joint, not for FM	£18	(section 9.1), PSSRU 2014 (182) (contact for 30 minutes from PSSRU 2010 (183))
Consultant visit: Rheumatology	152.08	Service code: 410, NHS reference cost 2015-2016 (184)
ER visits	148.34	Service code: 180, NHS reference cost 2015-2016 (184)
blood test	20	Wright et al. (185), price inflated to 2016 price (180)
CT scan	99, 70-121	Currency code: RD20A, NHS reference cost 2015-2016 (184)
MRI	146, 108-167	Currency code: RD01A, NHS reference cost 2015-2016 (184)
CBT	£52	PSSRU 2016 (180) (contact for one hour, PSSRU 2016 (180)
Pain consultant: first visit	£181	NHS reference cost 2015-2016 (184)
Pain consultant: follow-up visit	£225	NHS reference cost 2015-2016 (184)
Pain consultant: follow-up phone call	£20	NHS reference cost 2015-2016 (184)
* Unit cost estimates prior to 2016 price year were inflated using the Hospital and Community Health Services (HCHS) pay and prices index (180)		

Appendix 16. Long term effectiveness studies of PMS in FM/CWP

Published studies for PMS's long-term effectiveness in addressing FM\CWP are few and most have poor methodological design (106, 118, 225). A literature search of these studies was performed and five studies with a more than one-year follow-up (range: 15 months to 5 years) were summarised in Table 42 and discussed below (131, 159, 245, 246).

The longest follow-up periods (4 and 5 years) were observed in two studies published between 1996 and 1997 (245, 246); however, due to the small sample size (n=<17 in each arm), high drop-out rate (27-37%) and low methodological quality, both studies were excluded from the Cochrane review (118). The next longest follow-up period was two years, in two studies (131, 159). In the study by Eijk-Hustings et al., the positive effect of the intervention increased at two years when compared with the immediate post-intervention effect (159). However, the intervention included an aftercare meeting with the patients, which may be more intensive than Nottingham PMS intervention. In the other study, performed by Beasley et al. and discussed in the Chapter Four, the authors tested more than one PMS intervention and the effect were either maintained or slightly decreased, when compared with the post-intervention and nine month follow-up data (131). In summary, the results from Beasley et al. provide good quality data regarding the effectiveness of PMS at two-year follow-up. Studies performed with more than twoyear follow-ups have low methodological quality. Therefore, the attrition of effect assumption was applied after year two in the model based on data by Beasley and colleagues (131).

Table 42. Summary of studies for the long-term effectiveness of PMS in patients with CWP/FM

Study	Interventions, FU period	Baseline	Post intervention	FU	Comment
Wigers et al., 1996 (245)/	PMS 1 (stress management) for 8 wks (n= 13) PMS 2 (aerobic exercise) for 14 wks (n= 15) SC (n= 16), FU= 4 years	Pain intensity (VAS) PMS1=72 PMS2= 72 SC=65	Pain intensity (VAS) PMS1=64 PMS2= 62 SC= 72	Pain intensity (VAS) PMS1=67 PMS2= 64 SC=69	Data obtained from Cochrane review (118). Drop-out= 27% at 4yr Methodological quality is low; this study was excluded from the Cochrane review.
Lindh 1997 et al., (246)	PMS (individually prescribed) Control group is not clear FU=5 years	Return to work: 6 months: 40% vs. 55%; 1yr: 62% vs. 64%; 2yr: 72% vs.71%; 3yr: 75% 77%; 4yr:85% vs. 86%; 5yr: 87% vs 87%. Working at 6 months; 20% vs 27%; 1yr: 45% vs. 45%; 3yr: 55% vs 47%; 5yr; 58% vs 47%.			Data obtained from Cochrane review (118) Drop-out= 37% at 5yr. Methodological quality is low; this study was excluded from the Cochrane review.
Eijk-Hustings et al., 2013 (159)	PMS (sociotherapy+ physiotherapy+psychotherapy for 12 wks then aftercare meetings for 9 months), for 1 year (n=108) Aerobic exercise (AE) for 12 wks, (n=47) SC (n=48) FU= 2 years	**EQ-5D-3L (SD):** PMS=0.36 (0.03) AE=0.41 (0.05) SC= 0.51 (0.05) **FIQ (SD):** PMS=64.5 (1.4) AE=60 (2.1) SC= 55.4 (2.3)	**EQ-5D-3L (SD):** PMS=0.49 (0.03) AE= 0.47 (0.05) SC= 0.50 (0.04) **FIQ (SD):** PMS=55.1 (1.5) AE=53.2 (2.4) SC= 58.1 (2.3)	**EQ-5D-3L (SD):** PMS= 0.55 (0.03) AE= 0.54 (0.05) SC= 0.51(0.05) **FIQ (SD):** PMS=50.9 (2) AE=52 (3.2) SC= 56.2 (2.9)	The PMS intervention included aftercare meetings which may be more extensive than those in the setting of the present study. No details about the AE intervention if it was PMS or not.
Beasley et al., 2015 (131)	PMS1 (Telephone-delivered CBT (TCBT)+ UC) for 6 months PMS2 (Exercise + UC) for 6 months PMS3 (combined therapy: TCBT+ exercise+ UC) for 6 months UC FU: 9 months and 2 years	**EQ-5D-3L (SD):** PMS1= 0.730 (0.151) PMS2= 0.686 (0.209) PMS3= 0.681 (0.175) UC=0.649 (0.216)	**EQ-5D-3L (SD):** PMS1=0.723 (0.266) PMS2= 0.716 (0.208) PMS3= 0.737 (0.176) UC=0.688 (0.245)	**EQ-5D-3L (SD), 2 years:** PMS1=0.730 (0.242) PMS2= 0.712 (0.242) PMS3= 0.682 (0.238) UC=0.631 (0.315)	Other outcomes were evaluated.

BDI : Beck Depression Inventory, FU: follow-up period, PMS: pain management service, SC: standard care, VAS: visual analogue scale, wks: weeks.

Appendix 17. Testing the assumptions for OLS estimation

Background and rationale for the analysis

In order to rely on the results of Ordinary Least Square (OLS) in Chapter Six, some assumptions underlying OLS regression should be met. Without verifying that the data have met the assumptions, results may be misleading and biased. There are five basic assumptions made when performing and using OLS (208):

- Linearity - the dependent variable, the EQ-5D, can be calculated as a linear function of a specific set of independent variables plus an error term.
- Normality - the errors should be normally distributed
- Homogeneity of residuals' variance (homoscedasticity) - the variance around the residuals should be constant
- No multicollinearity- there is no linear relationship among the independent variables.
- Random Sample – sample is drawn randomly from the population. This assumption is not of concern for this analysis because the sample in Luciano et al. are assumed to be random sample of FM patients due to method of recruitment (211).

In this section, the results for testing the assumptions of the OLS will inform the validity of OLS models in Chapter Six in this thesis, and suggests what alternative regression models to adapt for mapping if there are violated assumptions.

Aims and objectives

The aims of this section was to assess the four OLS assumptions in order to inform the choise of regression model for the analysis in Chapter Six. The objectives were to test (1) Normality: test if the residuals impose normal distibution or not. (2)

Homoscedasticity: test if variance around the errors is constant or not (3) Multicollinearity: test if there are linear relations between independent variables in the model, and (4) Linearity: test if the relationship between the dependent and independent variables is linear or not.

Methods

Many graphical methods and numerical tests have been developed for regression diagnostics. Methods to test each of the four objectives are described below. All statistical test in this appendix was carried out using Stata 14. All Stata commands used in this section are obtained from http://www.ats.ucla.edu/stat/stata/webbooks/reg/chapter2/statareg2.htm and included within this section written in *italics.* In this analysis, the EQ-5D-3L tarrif score is the dependent variable. The independent variables included are presented within table 43. More details on the data is presented in Chapter Six.

Table 43. Summary of variables collected in the sample obtained to map the FIQR into the EQ-5D-3L

Variable	Description	Continous variable	Discrete or binary variable	comments
Dependent variable				
EQ-5D-3L tarrif score	Health- related quality of life	−0.654 (state worse than death) to 1 (full health)	-	Spain-Utility weighted tarrif score
Independent variable				
Age	Patient age	37-77 years	-	-
Gender	Gender of patient	-	1: female 2: male	
Education	Level of education	-	1 : Did not graduate from primary school 2: Primary school 3: Secondary school 4: University	-
Marital status	Marital status of patient	-	1: Single 2: Married/Living with a partner 3: Separated/divorced 4: Widowed	-
Living arrangement	Household living arrangements of patient	-	1: Living alone 2: Living with someone (spouse/partner/relative)	-
Work status	Work status of patient	-	1: Homemaker 2: Paid employment 3: Paid employment but on sick leave 4: Unemployed with allowance 5: Unemployed without allowance 6: Retired/pensioner 7: Others (e.g. student)	-
Years since diagnosis	years since patient diagnosed with FM	1-45 years	-	-
FIQR	The Revised fibromyalgia impact questionnaire	0 (no impact) to 100 (severe impact)	-	-

1- Methods to test the normality of residuals

The linear regression analysis requires the distribution of the residuals to be normal. This assumption can best be checked graphically using Kernel density plot *(kdensity)* with normal option requesting that a normal distribution be overlaid on the plo for comparisont. A statistical test for skewness, the asymmetry of the distribution, and kurtosis, the sharpness of the peak, using (***sktest)*** command was developed by D'Agostino et al (247). This test the null hypothesis that the residual is normally distributed at the 5% significance level. The Shapiro-Wilk W test ***(swilk)*** that is developed by Royston also can be used to test the hypothesis of residuals normal distribution (248).

2- Methods to test the Homoscedasticity

As the normality test, graphical and statistical tests are available assess the distribution of the variance around the residuals. The Residual-versus-fitted (RVF) plot ***(rvfplot)*** the residuals against the fitted, predicted, values. A reference line can be added at y=0 using the command (***yline(0)***). If the variance of the residuals is non-constant, then the residual variance is said to be "heteroscedastic"

The White's test (**imest**) and the Breusch-Pagan test (**hettest**) both test the null hypothesis that the variance of the residuals is homogenous. If the p-value is very small (at 5% significance level), we would have to reject the hypothesis and accept the alternative hypothesis that the variance is not homogenous.

3- Multicollinearity test

When there is a perfect linear relationship among the independent variables, the estimates for a regression model cannot be uniquely computed. Multicollinearity can be tested using the Variance Inflation Factor (VIF) test using ***(vif)*** command for Stata. VIF values greater than 10 are indicator for Multicollinearity.

4- Linearity test

Linearity is graphically assessed using locally weighted scatterplot smoothing line (LOWESS)using the command **(*lowess*)** with twoway scatter **(*twoway*)** with a linear fit ***(lfit).*** Another test can be used to assess the relation between the variables is the Augmented Component-Plus-Residual plot (***acprplot***). Any deviation of the lowess line from the linear line is an indicator for non-linearity.

Results

The results of assessing the four assumptions: normality, homoscedasticity, multicolinearity, and linearity for OLS estimation are described below.

1. Results from testing normality of residuals :

The Kernel density plot suggests that OLS model residuals are not normally distributed when plotted against a normal distribution (**Figure A.1**). Also, both results from the numerical ***sktest*** test and Shapiro-Wilk W test provide an evidence to reject the normality of the residuals at a 5% significance level; $p<0.001$.

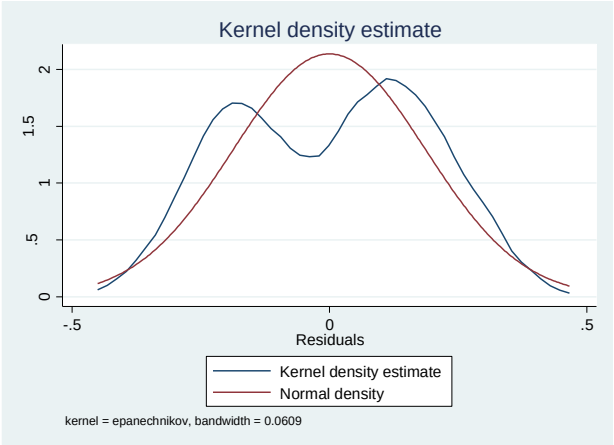

Figure A.1. Kernel density plot of the OLS model residuals against a fitted normal distribution

2. Results from testing the Homoscedasticity

Figure A.2 shows the results of the RVF plot for Homoscedasticity. The pattern of the residuals data points is a little narrower towards the right end, which may indicate a mild level of heteroscedasticity. Both statistical tests by White's and the Breusch-Pagan accept the hypothesis that the variance of the residuals are homogenous i.e. homoscedastic at p-value=0.177 and 0.758, respectively.

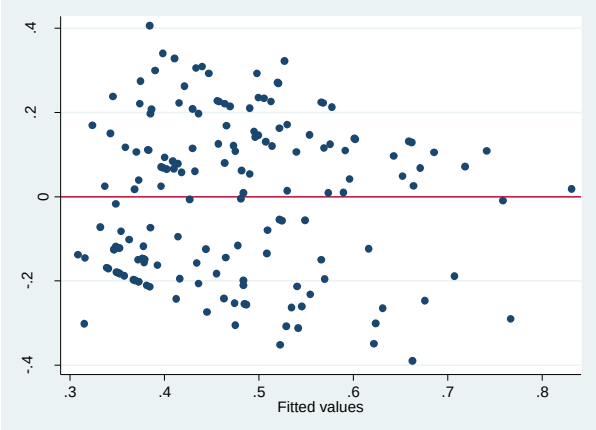

Figure A.2. RVF plot of OLS model residuals

3. Results from testing multicollinearity

The VIF test for multicollinearity is shown in Table 44. Result from mean VIF= 2.48 suggest that there is no collinearity between independent variables in the OLS model. The largest VIF for an individual variable is 8.93 (Marital status: married/living with a partner).

Table 44. Variance Inflation Factor (VIF) of the independent variables

Variable	VIF
FIQR total score	1.12
Gender (1: Female)	1.12
Age	2.48
Marital status (1: single)	
Married/Living with a partner	8.93
Separated/divorced	5.29
Widowed	4.77
Living arrangement (1: living with someone)	1.84
Education (1 : Did not graduate from primary school)	
2: Primary school	2.04
3: Secondary school	2.39
4: University	1.57
Work status (1: Homemaker)	
2: Paid employment	1.78
3: Paid employment but on sick leave	1.35
4: Unemployed with allowance	1.65
5: Unemployed without allowance	1.48
6: Retired/pensioner	1.60
7: Others (e.g. student)	1.55
Years since FM diagnosis	1.29
Mean VIF	2.48

4. Results from testing Linearity

A small degree of non-linearity between the EQ-5D-3L and FIQR is shown in **Figure A.3**. The LOWESS line in the scatter plot is deviated from the fitted linearity line. It is noteworthy to mention that although the relationship is non-linear, a distinction only visible in the right tale of the data plots.

The ACPR plot shown in **Figure A.4** indicates that there are mild levels of non-linearity between the dependent and independent variables. Logarithm transformations can be used for higher degrees of non-linearity to lessen the deviation from the fitted line.

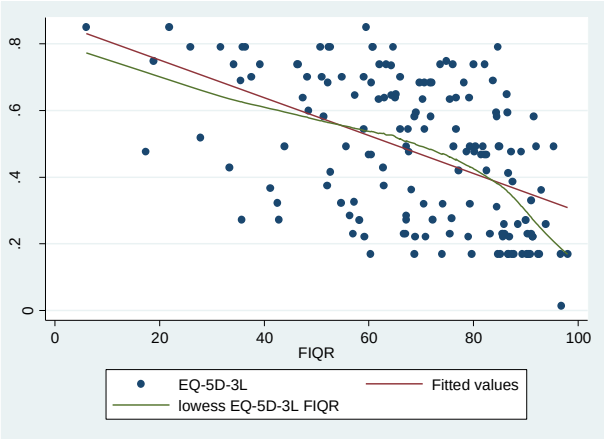

Figure A.3. Two-way scatter plot with locally weighted scatterplot smoothing line (LOWESS) of EQ-5D-3L and FIQR

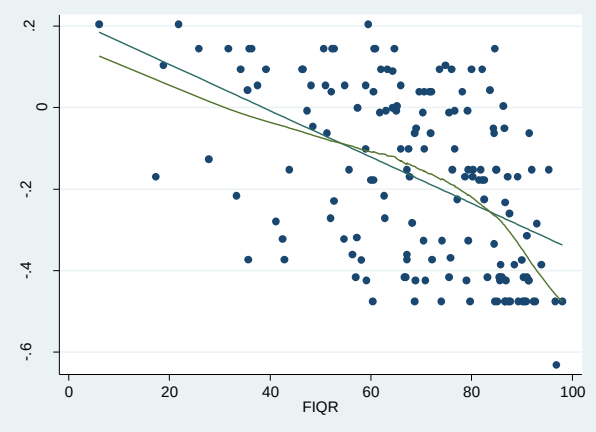

Figure A.4. Augmented Component-Plus-Residual plot (ACPR) of EQ-5D-3L Vs. FIQR

Conclusion

The results from assessing OLS model assumption between the dependent variable, the EQ-5D-3L and independent variables described in Table 42 show that the dataset had issues with non-normality and low degree of non-linearity. Homoscedasticity and absence of multicollinearity between independent variables were approved graphically and statistically. Many researchers believe that normality is required for OLS regression, this assumption is only required for valid hypothesis testing, i.e. it assures that the p-value for the t-test is valid, and not to obtained unbiased estimates of the regression (249). Also, it is recognised that the EQ-5D distribution violates the OLS regression assumptions, most mapping studies that have compared alternative models concluded that the OLS gives the best overall performance (200-202).

Although the results indicate that most of OLS assumptions were met, alternative regression models to the OLS were considered in Chapter Six to overcome the finite risk that may raise from violated assumptions.