Health Technology Assessment 2004; Vol. 8: No. 46

Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis

CJ McCarthy, PM Mills, R Pullen, G Richardson, N Hawkins, CR Roberts, AJ Silman and JA Oldham

November 2004

Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis

CJ McCarthy,* PM Mills, R Pullen, G Richardson, N Hawkins, CR Roberts, AJ Silman and JA Oldham

Centre for Rehabilitation Science, University of Manchester, Manchester Royal Infirmary, UK

* Corresponding author

Declared competing interests of authors: none

Published November 2004

This report should be referenced as follows:

McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*. Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis. *Health Technol Assess* 2004;**8**(46).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 94/39/14. As funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley
Series Editors: Dr Peter Davidson, Professor John Gabbay, Dr Chris Hyde, Dr Ruairidh Milne, Dr Rob Riemsma and Dr Ken Stein
Managing Editors: Sally Bailey and Caroline Ciupek

ISSN 1366-5278

© Queen's Printer and Controller of HMSO 2004

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to NCCHTA, Mailpoint 728, Boldrewood, University of Southampton, Southampton, SO16 7PX, UK.

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis

CJ McCarthy,* PM Mills, R Pullen, G Richardson, N Hawkins, CR Roberts, AJ Silman and JA Oldham

Centre for Rehabilitation Science, University of Manchester, Manchester Royal Infirmary, UK

* Corresponding author

Objectives: To establish the relative effectiveness and cost of providing a home-based exercise programme versus home-based exercise supplemented with an 8-week class-based exercise programme.

Design: The trial was a pragmatic, single-blind randomised clinical trial accompanied by a full economic evaluation.

Setting: Patients were randomly allocated to either home-based exercise or home exercise supplemented with class exercise programmes.

Participants: A total of 214 patients, meeting the American College of Rheumatology's classification of knee osteoarthritis, were selected from referrals from the primary and secondary care settings.

Interventions: Both groups were given a home exercise programme aimed at increasing lower limb strength, and endurance, and improving balance. The supplemented group also attended 8 weeks of twice-weekly knee classes run by a physiotherapist. Classes represented typical knee class provision in the UK.

Main outcome measures: Assessments of locomotor function, using a timed score of three locomotor activities, walking pain and self-reported disability with the Western Ontario and McMaster's Universities osteoarthritis index (WOMAC) were made. General health, lower limb strength, range of movement and compliance with exercise were also measured. Patients were assessed before and after treatment, and also at 6- and 12-month follow-ups. The economic evaluation looked at health service resource use and assessed cost-effectiveness by relating differential costs to differences in quality-adjusted life-years (QALYs) based on patients' responses to the EuroQol-5 Dimensions. Data were obtained at baseline, 1 month, 6 months and 12 months through face-to-face interviews and, where appropriate, examination of hospital medical records.

Results: Patients from the supplemented group demonstrated significantly greater improvement in locomotor function and decrease in pain while walking at all follow-ups. The supplemented group also demonstrated smaller but significant improvements in balance, strength, WOMAC score, and the physical function and pain dimensions of the Short Form-36. However, not all of these improvements were maintained over the 12-month follow-up period. There was no evidence that compliance with the home exercise programme was different or that total costs or mean QALY gains were significantly different between the groups. However, costs were slightly lower and QALY gains slightly higher in the group with the supplementary class-based programme. The economic evaluation suggests that supplemented programmes are likely to be considered cost-effective, although there is uncertainty around this estimate, with approximately 30–35% probability that the intervention would not be cost-effective.

Conclusions: The supplementation of a home-based exercise programme with a class-based exercise programme led to superior improvement in the supplemented group. These differential improvements were still evident at review 12 months after treatment had ceased. The additional cost of the supplemented group was offset by reductions in resource use elsewhere in the system. Compliance with the home exercise programme did not differ between the groups. Based on this evidence, the supplementation of a home-based exercise programme with an 8-week class-based exercise

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

programme can be confidently expected to produce small improvements in locomotor function and clinically important reductions in pain. It is recommended that future research investigates methods of increasing compliance with home exercise programmes and evaluates the impact of these interventions in the primary care setting, where most patients with knee osteoarthritis are managed.

Contents

List of abbreviations

ACR	American College of Rheumatology
ALF	Aggregate Locomotor Function
AP	anteroposterior
BMI	body mass index
BSR	British Society for Rheumatology
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CIH	change in health score
EQ-5D	EuroQol 5 Dimensions
EV	energy/vitality
Freq.	frequency
GMean ratio	ratio of geometric means
HP	health perception
ICC	intraclass correlation coefficient
ICER	incremental cost-effectiveness ratio
ICIDH	International Classification of Impairment, Disability and Handicap
ITT	intention to treat
LVCF	last value carried forward
MAR	missing at random
MCID	minimal clinically important difference
MH	mental health
ML	mediolateral
NMB	net monetary benefit
NSAID	non-steroidal anti-inflammatory drug
P	pain
PF	physical function
QALY	quality-adjusted life-year
RCP	Royal College of Practitioners
RCT	randomised controlled trial
RLM	role limitation – mental
RLP	role limitation – physical
SCICSTTT	Standing Committee for International Clinical Studies Including Therapeutic Trials
SD	standard deviation
SDD	smallest detectable difference
SEM	standard error of measurement
SF	social functioning
SF-36	Medical Outcomes Study Short Form 36 Health Survey
SRM	standardised response mean
TKR	total knee replacement
VAS	visual analogue scale
WOMAC	Western Ontario and McMaster's Universities osteoarthritis index
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Executive summary

Background

Exercises that strengthen the lower limb musculature have been shown to produce improvements in pain and locomotor function in patients with knee osteoarthritis. Physiotherapists often provide home- and class-based exercise programmes for patients with knee osteoarthritis; however, the effect of supplementing home-based exercise with class-based exercise has not been established.

Objectives

The study aimed to establish the relative effectiveness and cost of providing a home-based exercise programme versus home-based exercise supplemented with an 8-week class-based exercise programme.

Methods

Design

The trial was a pragmatic, single-blind randomised clinical trial accompanied by a full economic evaluation.

Subjects and setting

The subjects were 214 patients, meeting the American College of Rheumatology's classification of knee osteoarthritis, selected from referrals from the primary and secondary care settings. Patients were randomly allocated to either home-based exercise or home exercise supplemented with class exercise programmes.

Interventions

Both groups were given a home exercise programme aimed at increasing lower limb strength, and endurance, and improving balance. The supplemented group also attended 8 weeks of twice-weekly knee classes run by a physiotherapist. Classes represented typical knee class provision in the UK.

Main outcome measures

Assessments of locomotor function, using a timed score of three locomotor activities (walking, transferring and stair time), walking pain and self-reported disability with the Western Ontario and McMaster's Universities osteoarthritis index (WOMAC) were made. General health, lower limb strength, range of movement and compliance with exercise were also measured. Patients were assessed before and after treatment, and also at 6- and 12-month follow-ups. The economic evaluation looked at health service resource use and assessed cost-effectiveness by relating differential costs to differences in quality-adjusted life-years (QALYs) based on patients' responses to the EuroQol-5 Dimensions. Data were obtained at baseline, 1 month, 6 months and 12 months through face-to-face interviews and, where appropriate, examination of hospital medical records.

Results

Analysis involved the use of a longitudinal linear model analysis of covariance. Patients from the supplemented group demonstrated significantly greater improvement in locomotor function and decrease in pain while walking at all follow-ups. Pooled estimates of effect were –2.9 seconds [95% confidence interval (CI) –1.8 to –4.0] for locomotor function and 14.9 mm (95% CI –11.7 to –18.1) for walking pain, representing between-group differences of 12% and 27%, respectively. The supplemented group also demonstrated smaller but significant improvements in balance, strength, WOMAC score, and the physical function and pain dimensions of the Short Form-36 ($p < 0.05$). However, not all of these improvements were maintained over the 12-month follow-up period. There was no evidence that compliance with the home exercise programme was different or that total costs or mean QALY gains were significantly different between the groups. However, costs were slightly lower and QALY gains slightly higher in the group with the supplementary class-based programme. Thus, for most reasonable values of a decision-maker's willingness to pay for an additional QALY, the addition of the class-based programme is likely to be cost-effective. There is considerable uncertainty around this estimate and a probability of approximately 30–35% that the intervention is not cost-effective.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Conclusions

The supplementation of a home-based exercise programme with a class-based exercise programme led to superior improvement in the supplemented group. These differential improvements were still evident at review 12 months after treatment had ceased. The additional cost of the supplemented group was offset by reductions in resource use elsewhere in the system. Compliance with the home exercise programme did not differ between the groups.

Implications for the health service

Based on this evidence, the supplementation of a home-based exercise programme with an 8-week class-based exercise programme can be confidently expected to produce small improvements in locomotor function and clinically important reductions in pain. Cost-effectiveness is somewhat less certain, although at levels of willingness to pay for an additional QALY of greater than £10,000, the probability that supplemented programmes would be cost-effective is around 70%.

Recommendations for future research

It is recommended that future research investigates methods of increasing compliance with home exercise programmes and evaluates the impact of these interventions in the primary care setting, where most patients with knee osteoarthritis are managed.

Chapter 1

Introduction: osteoarthritis of the knee

Introduction to osteoarthritis

Osteoarthritis is the single most important cause of disability and limitation of activity in elderly people in the UK.[1] The knee is the most often affected weight-bearing joint;[2] consequently, knee osteoarthritis is an extremely common cause of severe pain and disability in the community.[3] One-third of people 63–94 years of age are affected by knee osteoarthritis that often limits the ability to rise from a chair, comfortably walk and use stairs.[4] In addition, knee osteoarthritis causes knee pain that can range from mild to extreme severity.[5]

"Osteoarthritis can be defined as a slowly progressive monoarticular disorder of unknown cause and obscure aetiology. The condition occurs late in life, principally affecting the hands and large weight-bearing joints, and is characterised by pain, deformity, enlargement of the joints and limitation of motion. Pathologically the disease is characterised by focal erosive lesions, cartilage destruction, subchondral cyst formation and large osteophytes at the margins of the joint".[6]

Features of osteoarthritis have been described across the animal phylogenic spectrum, in birds, reptiles and mammals. It is ubiquitous to the natural world.[7] Osteoarthritis is one of the leading causes of disability in western industrialised countries and is associated with significant health and welfare costs.[8] At a personal level, the indirect costs of osteoarthritis are considerable. It is responsible for losses in work and social activities and for difficulties in performing self-care tasks.[8]

Epidemiology of knee osteoarthritis

It is estimated that, in the UK, 7.5% of people over the age of 55 years have some knee pain and disability associated with radiographic evidence of osteoarthritis, and that 2% have severe problem.[9] The largest and most comprehensive radiological study undertaken was performed in the Dutch district of Zoetermeer, where over 6000 subjects were surveyed.[10] The authors demonstrated that prevalence of knee osteoarthritis in women rose from around 5% in the 60–70-year age group to over 25% in the 80 years and older group. In men prevalence remained around 5% from 60 years upwards. Knee osteoarthritis was significantly more prevalent than hip or distal interphalangeal joint osteoarthritis.

One recent study[11] reviewed the literature regarding incidence and prevalence of knee pain, disability and radiographic osteoarthritis in the general population, and also data related to primary care consultations. The authors found that during a 1-year period 25% of people over 55 years had experienced a persistent episode of knee pain, of whom about one in six had consulted their GP about it. The authors concluded that the prevalence of painful disabling knee osteoarthritis in the UK for people over 55 years was 10%, of whom one-quarter were severely disabled.

Burden of the disease

Community-based studies have shown that joint pain and disability in older people depend as much on factors such as depression and isolation as they do on the severity of joint damage.[12] Most mild osteoarthritis does not progress to severe joint damage requiring surgery;[13] however, the economic cost of knee osteoarthritis has been commonly estimated by analysis of numbers of total knee replacements performed annually. This does not provide a representative picture of the costs of knee osteoarthritis as only one major direct cost to healthcare providers is evaluated.

The costs of physiotherapeutic management of knee osteoarthritis are unknown. Physiotherapy treatment for knee osteoarthritis is commonly provided on an individual or a class-based basis and home exercise programmes are most commonly provided for patients.[14] Although the provision of treatment in classes enables more patients to be treated in the available time than individualised treatment, the costs and economic benefits of physiotherapy treatment for knee osteoarthritis have not been established. As the prevalence of knee osteoarthritis is likely to increase in the future, with the shift in the population demographic towards an ageing population,[15] these costs could be considerable.

Direct costs or healthcare utilisation and expenditure due to osteoarthritis are high. Each

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

GP in the UK can expect approximately 117 consultations annually involving osteoarthritis, with 35 of these involving people consulting with this problem for the first time.[16] In 1996 nearly 35,000 total knee replacement (TKR) operations were performed in the UK.[17] Two-thirds of these operations were for the treatment of knee osteoarthritis.[9,18]

Osteoarthritis is so common in the developed world that it is the fourth highest impact condition in women and the eighth most important in men.[19] In the USA osteoarthritis was second only to ischaemic heart disease as the primary diagnosis leading to the awarding of Social Security Disability Insurance benefits.[20] In the 1996 annual report of the Chief Medical Officer of the Department of Health,[21] 20% of all reported causes of disability were found to be arthritic in nature, while in a self-reported disability population survey, osteoarthritis was involved in the disability reported by 25% of 60–74-year-olds and by 65% of over-75-year-olds.[22] Population forecasts predict substantial increases in the elderly population over the next 30 years,[22] with life expectancy increasing to 85–87 years by the middle of the twenty-first century.[15] There is an increase in incidence and prevalence of knee osteoarthritis with increasing age, and these two factors combined will lead to an exacerbation of the economic burden of managing knee osteoarthritis.[20]

Current treatment of knee osteoarthritis

Several eminent clinical bodies have produced guidelines for the treatment of knee osteoarthritis. In 1993 the joint working group of the British Society for Rheumatology (BSR) and the Royal College of Physicians (RCP) published guidelines for the management of hip and knee osteoarthritis.[23] The American College of Rheumatology (ACR) published guidelines for the medical management of knee osteoarthritis in 1995 and updated these guidelines in 2000.[24,25] In 2001 the task force of the Standing Committee for International Clinical Studies Including Therapeutic Clinical Trials (SCICSTTT) produced European League Against Rheumatism (EULAR) recommendations for the management of knee osteoarthritis.[26] These guidelines placed emphasis of treatment on patient education, pain relief and exercise. The management options recommended by the groups are listed in *Table 1*.

TABLE 1 *Non-surgical management of knee osteoarthritis*

ACR	BSR/RCP	EULAR SCICSTTT
Pharmacological		
Non-opioid analgesics	Analgesics	Analgesics (paracetamol)
NSAIDs	NSAIDs	NSAIDs
Opioid analgesics		
Topical analgesics		Topical analgesics
Intra-articular steroid injections Hyaluronic acid	Intra-articular steroid injections	Intra-articular steroid injections Hyaluronic acid
Non-pharmacological		
Patient education Self-management programmes	Patient education	Patient education
Weight loss	Weight reduction	Weight reduction
Stretching	Exercise physiotherapy	Stretching
Quadriceps strengthening exercises		Quadriceps strengthening exercises
Assistive devices for ambulation		Assistive devices for ambulation
Joint protection and energy conservation Assistive devices for function Aerobic exercise programmes	Modification of mechanical factors (footwear, stick use)	Modification of mechanical factors (footwear, stick use)

NSAID, non-steroidal anti-inflammatory drug.

Rehabilitation treatment of knee osteoarthritis

Physical treatments, provided by therapists, are advocated in the management of knee osteoarthritis by the BSR, the ACR and the SCICSTTT.[23–26] Physiotherapeutic treatment, particularly exercise, has been part of the management of knee osteoarthritis for over a century,[27] and in a recent study was shown to be the second most frequently prescribed treatment for knee osteoarthritis after oral medication.[28]

Patient education programmes

There is some evidence that health promotion, teaching self-care skills and methods of modifying risk factors have a beneficial influence on patients symptoms and progress of the disease.[29] In a recent study,[30] 211 inner-city patients were randomly allocated to either an education programme or a standardised public education video on arthritis. The patients receiving the education programme had significantly lower pain and function scores throughout the year of postintervention follow-up. The authors followed up this study in 1999 with a paper describing the cost utilisation savings of the programme and concluded that 80% of the initial outlay costs for the programme would be recouped by reduced primary care utilisation.[31] A similar UK-based arthritis self-management study also demonstrated significant reductions in reported pain, fatigue and anxiety at 4-month[32] and 12-month follow-up.[33] Osteoarthritis sufferers made up 44% of the sample population. A recent Dutch study demonstrated that health education in combination with an exercise programme significantly reduces pain and increases self-efficacy and knowledge in patients with knee osteoarthritis.[34]

Educational advice is considered essential by the ACR, the BSR and the RCP,[23–26] and is considered by patients to be an important part of management.[28] Educational components are commonly included in knee osteoarthritis treatment programmes provided by physiotherapists.[14,35]

Exercise treatment

Exercise is the only physical modality that has been consistently found to be of value in osteoarthritis.[36] It is recommended in the management of knee osteoarthritis by all professions involved in the rehabilitation of sufferers,[23–25,37,38] and promoted by arthritis charities as a valuable treatment to patients.[39]

Four eminent professional bodies have produced treatment guidelines that recognise the multidimensional causes and effects of knee osteoarthritis. These bodies have recommended a multidimensional treatment approach that emphasises education, self-care management, simple drug therapy and particularly exercise for the majority of patients who have not progressed to severe disease.[23–26] When a clinical presentation is varied the treatment goals for health professionals and patients are also varied. The many treatments of knee osteoarthritis are ubiquitously aimed at reducing symptoms and regaining function, as no treatment has been shown to 'cure' the condition.[40] Recently, a shift in treatment paradigm has been recommended from the overemphasis of drug therapy towards more education, self-management and exercise-based therapies in the treatment of less severe knee osteoarthritis.[23,25,26,41,42]

Effects of exercise in arthritis

Several studies have indicated that people with osteoarthritis or rheumatoid arthritis demonstrate lower levels of muscle strength,[43] aerobic conditioning[44] and functional range of movement[45] than the healthy population. Arthritis is a highly prevalent condition that leads to pain and disability. A significant portion of the disability is due to loss of physical capacity, which is in part correctable through exercise training programmes.[46] After several years of investigation, the principle that exercise offers benefit to arthritis patients is under little debate.[47,48]

Several studies have demonstrated effective reduction of pain and anxiety with improved endurance and aerobic fitness after aerobic exercise programmes.[49–51] Other studies have shown similar degrees of improvement in the same outcomes with progressive resistance training programmes.[52–56] Improvement in walking ability has ranged from 16 to 27%,[50,57] with pain reduction ranging from 9 to 33%.[37,58]

Exercise and knee osteoarthritis

Exercise therapy has formed one of the mainstays of treatment for knee osteoarthritis for many years. Numerous authors have investigated the treatment of knee osteoarthritis with exercise in the past 20 years, with varying conclusions. Questions have been asked about the effectiveness, efficacy and safety of exercise therapy for treatment of knee osteoarthritis. These questions have been prompted by the need for rigorous randomised controlled trials (RCTs) establishing causal relationships between exercise treatment

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

and the pain and functional incapacity suffered by patients with osteoarthritis of the knee. In recent years RCTs have been conducted that, when collectively analysed, go some way to answering some of these questions.[3,57] It would appear that exercise therapy is beneficial for patients suffering from knee osteoarthritis. However, the degree to which exercise is beneficial varies according to the exercise programme undertaken.[37,59]

Exercises have been used for the treatment of osteoarthritis of the knee for many years.[27] The evidence provided by the literature reviewed suggests that exercise provision for patients with knee osteoarthritis reduces the pain experienced and the functional incapacity suffered by a small to moderate degree.[60] The improvements experienced following exercise treatment decline with time, but may still be evident at follow-up, up to 18 months post-treatment.[57] Exercise treatment, be it non-weight bearing or weight bearing, has only a small risk of exacerbating the patient's symptoms or causing injury when provided by trained professionals.[60] Furthermore, there is no evidence that moderate-intensity weight-bearing exercises, of the type provided in hospital-based settings, accelerate the disease process.[60]

Following a recent systematic review of the available literature,[61] it would appear that the recommendation of exercise treatment for patients with osteoarthritis of the knee should be supported. Furthermore, those exercises that are weight bearing, function mimicking and strengthen the quadriceps femoris muscle group are the most effective forms of exercise to provide. Many of the trials in the literature are flawed and more work is required to establish optimum types, frequency, duration, intensity and the settings of exercise programmes for patients with knee osteoarthritis. What is specifically unknown is whether exercise should be performed by patients individually, at home, or undertaken in a class-based setting. In addition, what are the long- and short-term effects of supplementing a home-based, individual exercise programme with class-based exercise, which is common clinical practice by physiotherapists in the UK? In Chapter 2 the methods of a study aimed at answering these questions will be described.

Chapter 2
Methodology

Need for the study

From an analysis of the available literature, it was evident that an important question regarding the effectiveness of exercise in the treatment of knee osteoarthritis remained unanswered. The effectiveness of the common clinical practice of supplementing a home exercise programme with a class-based exercise programme had not been established. The provision of exercise is the most common method of managing knee osteoarthritis patients by physiotherapists.[14] However, the lack of evidence to guide provision of exercise represents a significant problem for patients and clinicians, as best practice has not been established and thus current treatment provision may not be effective or clinically efficient.

From consultations with clinicians in the field, it became apparent that the supplementation of a class-based exercise programme with a home exercise programme is the clinical practice of UK physiotherapists. Physiotherapists do not teach patients to exercise in classes and then not recommend that they exercise at home. Physiotherapists either give patients solely home exercise or the home exercises supplemented by a 'knee class' programme. Not recognising this practice would have compromised the external validity of the design and resulted in a trial that had little impact on clinical practice. Thus, a pragmatic design was chosen to evaluate the relative effectiveness of the two methods of provision.

Aims and objectives

Aims of the study

- To compare the clinical effectiveness and cost-effectiveness of supplementing a home exercise programme with a class-based exercise programme against home exercise alone, in the treatment of knee osteoarthritis.
- To evaluate the effect of the two interventions on compliance with home exercise.

Objectives of the study

- To establish the size of any mean difference between the interventions on measures of locomotor function, pain, general health and physical impairment.
- To establish the effect of the two interventions on compliance with home exercise at follow-up.
- To assess the cost-effectiveness of the programme and to estimate the probability of each intervention being cost-effective at various levels of decision-makers' willingness to pay (WTP) for a quality-adjusted life-year (QALY).

Primary research question

Does supplementing a home exercise programme with a class-based programme result in greater improvement in walking pain and locomotor function 12 months after the end of contact with the physiotherapist?

Design

There is general consensus that RCTs provide the most secure basis for valid causal inferences about the effects of treatment.[62,63] There are two main types of RCT: explanatory and pragmatic. Explanatory trials are natural extensions of laboratory studies and evaluate the efficacy of one treatment compared with another, investigating the mode of action of a treatment in detail. Pragmatic trials evaluate the effectiveness of a treatment policy rather than the treatment itself; they are not concerned with how the treatment works but whether it works in clinical practice, and allow for the variations between subjects that occur in real clinical situations.[64] This trial was a pragmatic investigation of the relative effectiveness of two commonly adopted methods of providing exercise treatment to patients with knee osteoarthritis.

Subjects

The study population was intended to represent the heterogeneous population of patients with knee osteoarthritis who are typically referred to physiotherapists for exercise treatment. Referrals were from typical sources in clinical practice: orthopaedic and rheumatology clinics of local hospitals and local GPs. Medical practitioners working in these areas were informed of the trial

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

by postal information sent to them at 3-monthly intervals. In addition, during the recruitment period of the trial an article describing the ongoing research was published in a local newspaper. This led to increased awareness of the trial and increased referral rates, but also introduced a subgroup of patients who had approached their own GP to seek referral for treatment.

Inclusion criteria

Subjects were included, following an assessment by the trial's lead investigator, if they met the ACR clinical diagnostic guidelines[40] and none of the exclusion criteria detailed below. Subjects were physically assessed by the trial's lead investigator using a Maitland system of examination to reduce the risk of the patient's knee pain being referred from sources such as the lumbar spine, hip and sacroiliac joints.[65]

Subjects were selected based on the clinical assessment criteria of the ACR. The sensitivity and specificity of these criteria are 89% and 88%, respectively,[40] and have been shown to have high intra-rater reliability.[66] All patients had undergone knee radiographs before referral to the trial and had been informed by their referring doctor (rheumatologist, orthopaedic surgeon or GP) that, on the evidence of their X-rays, they had 'arthritis' of the knee. The inclusion of radiological evidence of osteophytes to the ACR clinical criteria increases the sensitivity to 94%, with specificity remaining at 88%.[40] It is reasonable to assume that, using this method of selection, patients had at least an 88–89% chance of having knee osteoarthritis.

Clinical criteria for knee osteoarthritis diagnosis (adapted from ACR criteria[67]):

- knee pain: subjects were eligible if they had complained of pain in or around the knee for most days in the previous month
- referred following knee radiograph showing knee osteoarthritis; and
- at least three of the following six clinical features:
  - age > 50 years
  - stiffness > 30 minutes upon waking
  - crepitus
  - bony tenderness
  - bony enlargement
  - no palpable warmth.

Exclusion criteria

The exclusion criteria are listed below. These criteria were selected after critically reviewing the literature in this area and selecting the most appropriate criteria to accentuate the external validity of the trial. The criteria enabled the inclusion of a heterogeneous sample representative of the patients commonly referred to physiotherapists for exercise treatment in the UK.

Exclusion criteria (based on a review of the relevant literature[60]):

- any evidence of symptomatic back or hip disease (i.e. pain in or around the back or hip joint severe enough to interfere with the exercise programmes)
- if the knee osteoarthritis was secondary to inflammatory arthritis, specifically rheumatoid arthritis
- any significant symptoms affecting the ankles or feet that would interfere with the exercise programmes
- any demonstration on physical examination that the patient's knee pain was originating from a proximal source such as back or hip
- patients unable or unwilling to attend for treatment at the physiotherapy department
- patients with significant psychiatric or general medical morbidity that would preclude either their undertaking the exercises or their understanding of the nature of the exercise treatment
- intra-articular steroid injection, in the knee, within 3 months.

Sample size

Aggregate Locomotor Function score

Based on work by Hurley and Scott,[37] and after piloting the Aggregate Locomotor Function (ALF) measure with patients with knee osteoarthritis, it was estimated that a sample size of 76 in each group would have 80% power to detect a difference of 4 seconds (20%) in ALF between the class and home exercise groups, assuming that the common standard deviation (SD) was 8.7 using a two group *t*-test with a 0.05 two-sided significance level.

A 15–20% dropout rate at short-term follow-up, immediately after treatment, and 30% at 6 months' follow-up was expected. These dropout levels have been described, for similar trials, as the maximum rates that can be accepted without rendering the trial invalid.[60] Thus, to obtain adequate power for both per protocol analysis[68] and intention to treat (ITT) statistical analysis,[68] 100 patients were recruited to each group. This target was thought to be achievable within the time allocated to

recruitment. Sample size estimation was performed with nQuery Advisor (Version 3.0) software.[69]

Ethical approval

Ethical permission for the trial was obtained from the Central Manchester HealthCare Trust's local ethics committee. At initial assessment patients were interviewed by the trial's lead investigator and given an information sheet, and written consent was obtained from willing participants after they had been given adequate time for consideration.

Assignment

Subject allocation was carried out using a computerised minimisation algorithm built into an access (Microsoft Corporation) database. To control for a number of important prognostic factors,[70] stochastic minimisation was used to allocate patients. This provided some protection against chance bias due to baseline imbalance, as is consistent with the recommendation that baseline variables of prognostic value should be identified and considered in the randomisation process to clarify post hoc analysis.[71]

Important prognostic factors, given equal weighting in subsequent analysis, were identified as obesity [body mass index (BMI) ≥ 30] and gender, as the risks of increased rate of disease progression are significantly raised in obese patients and females.[10,72] The third factor in the minimisation process involved allocation of equal numbers of patients who were to undertake core and full assessments. The rationale for this design feature is detailed later in this chapter (section 'Participant flow and follow-up', p. 13).

Blinding and concealment

Owing to the type of intervention being evaluated, this trial was an open trial. To protect against bias, outcome assessments were made blind to allocation.[73] This design feature allowed the patients to know which of the two treatment programmes they were receiving while preventing the trial's lead investigator from knowing this information until the trial steering group had agreed to break the code (i.e. unblind the trial) after all follow-up data had been gathered. To achieve effective blinding the following design features were incorporated into the trial design.

- The intervention was provided by a physiotherapist other than the trial's lead investigator.
- The lead investigator provided subjects' details to the trial data manager, who used a computerised, password-secured randomisation system (Microsoft Access) to allocate patients, at a location separate from the trial investigator's place of work.
- The physiotherapist providing the intervention was given a sealed envelope containing the allocation schedule for patients.
- Subjects were instructed not to mention the treatment they had received to the lead investigator.
- Subjects were instructed to direct any queries or concerns regarding treatment to the physiotherapist providing treatment and not the lead investigator.
- Data regarding compliance and attendance were forwarded directly to the trial data manager in sealed envelopes and not to the trial's lead investigator.

Primary outcome measure

Patients with knee osteoarthritis suffer primarily from reduced locomotor functional capacity[5,7,74] and thus the primary outcome measurement of this study was a timed measure of locomotor function.

ALF score

Physical dysfunction can be assessed in many ways. Two common approaches are the use of self-evaluation questionnaires such as the Western Ontario and McMaster's Universities osteoarthritis index (WOMAC),[75] and the use of performance observation[76] such as timed walking tests[77] and the timed up and go test.[78] Both methods have specific advantages and disadvantages. It has been stated that observational methods provide information about a patient's 'actual' state of disability and have the advantage of not being influenced by subjective factors, whereas self-evaluation methods reflect the patient's opinion of their disability.[79] Although it seems unlikely that the physical performance of testing procedures is completely unaffected by the patient's subjective influence on the test,[80] it has been argued that the two methods measure two different dimensions of disability.[81] One helpful classification that may clarify this issue is adapted from the International Classification of Impairment, Disability and Handicap (ICIDH) model.[80] While the activities comprising the ALF score can be classified as

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

'simple activity', the outcomes reported by self-reported questionnaires such as the WOMAC represent 'complex activity'. Simple activity concerns the performance of a set of functions that form a prerequisite of purposeful functional activities such as walking, transferring and stair ascent/descent, whereas complex activity concerns the performance of purposeful functional activity such as dressing and housekeeping.[80]

Observational methods have been shown to demonstrate good criterion-related validity with self-evaluation methods of disability, particularly when assessing mobility,[79] but the degree of sensitivity and specificity to change of both approaches has not been fully established. However, observational methods are considered to provide measures that are less influenced by patient expectation of treatment effect,[82] and provide measures of disability that are slightly less sensitive than, or as sensitive as[76] self-evaluation methods, while being more specific to mobility-related disability changes.[81]

Objective assessment of locomotor function of timed walking, stair ascent and descent, and transferring to and from a chair has been used by several investigators in the field of knee osteoarthritis.[3,34,37,57] Hurley and Scott aggregated the times of these individual activities to form one score with the rationale that "any single test imparts little information about the patient's overall functional ability, and that by aggregating the time of the activities a better objective assessment of the patient's overall functional capabilities can be obtained".[37]

Eight-metre walk time

The measurement of gait speed has been used to measure treatment efficacy, predict disability and evaluate functional capacity.[77,83,84] Gait speed decreases with age, with maximum speed declining more steeply than comfortable gait speed.[83] Subjects with knee osteoarthritis have been shown to have reduced walking speeds compared with age-matched normals,[45] with obese patients with knee osteoarthritis having further reductions in speed.[85] The measure has been shown to have high test–retest reliability in middle-aged adults,[86] and in elderly patients with knee osteoarthritis[77,87,88] when instructed to walk 8, 10 or 13 m at their own comfortable and preferred pace. Comfortable walking speed has been shown best to represent overall walking performance[89] and has been recommended as a measure of locomotor function.[83] It has been shown to be both a reliable and valid measure in patients with knee osteoarthritis, and does not have a significant learning effect that requires a training visit before collection of baseline data.[83,90]

Procedure

The patients were asked to walk, at their own naturally preferred, 'comfortable' pace, across the floor of the physiotherapy gymnasium. Following the recommendations of Hirokawa,[91] a 10-m stretch of floor was used. An 8-m distance was marked on the gymnasium floor. Timing of the central 8 m allowed one or two steps at either end of the walk for untimed acceleration and deceleration, a process that has been shown to increase test–retest reliability.[91] The time taken to complete the distance was measured using a handheld stopwatch (Zeon, UK). Patients were permitted to use walking aids if they required them. Three repetitions of the walk were undertaken and the times recorded. The mean time was calculated and used for subsequent analysis.

Stair ascent and descent time

Stair ascent and descent is a function that patients with knee osteoarthritis find painful and difficult to perform.[46,92,93] Large moments are generated at the knee during ascent and particularly descent of stairs,[94] the magnitudes of which are much greater than during level walking. The ability to climb stairs has been strongly correlated with leg extensor power and ability to transfer from sitting to standing in the elderly.[95] To achieve stair climbing, frail, elderly subjects must produce their maximum available leg power.[95] Consequently, stair climbing is a function rapidly lost with the reduced leg power associated with knee osteoarthritis.[96] The measurement of timed stair ascent and descent has been shown to have high test–retest reliability in an elderly population,[97] and has been used by several authors as a measure of treatment efficacy in knee osteoarthritis.[37,57,58]

Procedure

Patients were asked to ascend and then descend seven steps (four 15-cm and three 20-cm steps). Patients were instructed to undertake this task at their naturally preferred, comfortable pace. The method that the patient used to negotiate the stairs was recorded (i.e. whether they used alternate legs, used the banisters or always led with one leg). Patients were permitted to use the two banisters if they felt it necessary, as the use of banisters has been shown not to affect times.[95] Patients were timed using a handheld stopwatch and repeated the test four times. The mean of the four repetitions was calculated and used for

subsequent analysis. Four repetitions were used as the stairs used had different height steps, and thus going over the steps in one direction and then the other ensured that the patients ascended and descended the different height steps twice.

Transferring from sitting to standing time

"For independent mobility, one generally must be able to perform the basic mobility skills of getting in and out of bed and chair, on and off a toilet and walking a few feet".[78] These basic mobility skills are used in the performance of a timed transferring test.[78] The test requires the patient to rise from a chair, walk to a line on the floor 2 m away, turn, return and sit down again. The measure has been shown to correlate strongly with gait speed and self-reported functional capacity[78,98] and to correlate negatively with increasing age[99] and balance ability.[100] The measure has been shown to have high test–retest reliability[78,97] in an elderly population [intraclass correlation coefficient (ICC), 0.98].

Procedure

Patients were asked to walk, at their own natural pace, a distance of 2 m to a chair and sit down, then immediately stand up and walk back to the start. Patients were timed using an infrared beam sprint timer system (Cranlea Instruments, Birmingham, UK), as they approached and retreated from the chair. The chair had no arms and a seat height of 0.46 m, typical of a toilet seat height.[90] Patients undertook three timed repetitions, the mean of which was calculated and used for subsequent analysis.

The ALF score was then calculated by summation of the three timed scores. In instances where individual components of the score were not completed the reciprocal score could be used, thereby scoring missing data as zero. The ALF score was tested for reliability and validity during piloting.

Secondary outcome measures

To investigate more comprehensively the effects of the two exercise programmes on patients, a series of secondary outcome measures was included to provide information regarding self-reported functional capacity and the physical components of function.

Visual analogue pain score

The visual analogue scale (VAS) is a simple and frequently used method for the assessment of variations in intensity of pain,[101] and has been widely used in human clinical and psychological research to assess subjective states.[102] A VAS consists of a 10-cm line, the ends of which are marked with semantic opposites (e.g. no pain and the worst pain imaginable), and is applied by asking the patients to mark a point on the line between the two extremes that relates to their experience. Although there is debate about the measurement level of this instrument it is considered by many to present data that are interval and continuous rather than discrete.[68] Much evidence has been produced to establish the reliability and validity of the VAS in the assessment of pain,[101] in the assessment of knee conditions[103] and with elderly patients.[102] Although the VAS does not provide the same degree of content validity as more detailed questionnaires it is an adequate assessment tool for assessment of pain in activity-specific situations.[5,104] Unfortunately, the VAS has also been shown to be sensitive to subject bias, particularly when subjects are able to compare their current responses with previous ones.[101] However, if comparison of current response with previous response is prevented, the use of VAS in the assessment of pain associated with knee osteoarthritis has been widely recommended and adopted in osteoarthritis clinical trials.[105]

Procedure

Patients were asked to place a mark on a 10-cm line that best represented the degree of pain they had experienced, in the past 7 days, while walking on a flat surface. Subjects were not permitted to see previous scores. Scores were established by measuring, from the zero point, the distance to the mark in millimetres.

WOMAC

The WOMAC is a tridimensional, disease-specific, self-administered health status measure.[106] The index consists of 24 questions (five pain, two stiffness and 17 physical function dimensions) and is available in Likert and VAS scaled formats. The index has undergone two major validation studies[106,107] and been shown to fulfil conventional criteria for face, content and construct validity, and to be reliable and responsive.[108] The WOMAC has been widely used in clinical trials with knee osteoarthritis,[109] and has been shown to be more responsive to change than the Medical Outcomes Study Short Form 36 Health Survey (SF-36),[108] as the dimensions of the index have been specifically designed for osteoarthritis patients.[75] In a recent report of the international standing committee investigating clinical trials response criteria, the WOMAC was recommended as a primary outcome

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

measure for future clinical trials of hip and knee osteoarthritis.[110] Changes in WOMAC score of 20–25% are considered clinically important.[111]

Procedure
Patients were not permitted to see previous responses. Patients completed the forms by themselves without assistance from the lead investigator and were asked to relate their responses to the last 48 hours. The Likert scale version (LK3.0) of the questionnaire was used. Forms were entered onto the trial database. Missing data and scoring procedures followed the WOMAC user guidelines.[75]

SF-36
The SF-36[112] is a 36-item questionnaire that measures health functioning on eight scales and is among the most widely used measures of quality of life in studies of patients and populations.[113] The questionnaire is generic and provides a general insight into patients' health.[114] A recent large-scale (n = 1016) study investigating the reliability and validity of the SF-36 when used with patients with osteoarthritis or rheumatoid arthritis has shown the health survey to have high reliability for its eight scales (median coefficient = 0.84), high internal consistency and high item discrimination validity.[115] The use of the measure with subjects with knee osteoarthritis has been widely recommended and adopted in many clinical trials.[1,105,114–116]

Procedure
Subjects were not permitted to see previous responses. Subjects completed the questionnaires themselves with no assistance from the lead investigator. Missing data and scoring procedures followed the SF-36 user guidelines.[112]

EuroQol
The EuroQol 5 Dimensions (EQ-5D) is a health index designed for use in evaluative studies and policy research, and is intended to complement other forms of quality of life measures.[116] The questionnaire has two sections. The first part consists of five questions covering the dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three levels of response. The second section consists of a 20-cm vertical VAS ranging from best imaginable health state to worst imaginable health state.

The EuroQol has undergone several validation studies with arthritic subjects, and has been shown to be sufficiently reliable and responsive and to contain sufficient construct validity to be used in clinical trials involving arthritic subjects.[117,118] Some authors have expressed some concerns over the instrument's crude discrimination ability and restricted responsiveness, and the non-normal distribution of scores observed.[119] However, the use of the instrument has been particularly recommended when researchers wish to undertake an economic evaluation as part of a trial.[1]

Procedure
Subjects were not permitted to see previous responses. Subjects completed the questionnaires themselves with no assistance from the lead investigator. Missing data and scoring procedures followed the EuroQol user guidelines.[120]

Physical components of function
Muscle strength
Lower limb muscle strength has been shown to be an important correlate of locomotor function,[121] with isometric muscle strength being used by several investigators as a reliable and valid method of assessing exercise treatment.[52,53,55,122,123]

Procedure
To test maximum voluntary isometric extension, patients were positioned in the chair of a Biodex Dynamometer (Biodex, Shirley, NY, USA) with hip flexion fixed at 90 degrees and the knee angle set at 45-degree flexion. The more painful knee was tested. To ensure that the patients maintained the 45-degree angle, the operator placed an arm under the knee to act as a popliteal restraint. Patients pushed into the footplate of a leg press attachment, without pushing the popliteal surface of the knee into the operator's arm and beyond 45 degrees. Patients had two practice contractions before data collection to familiarise themselves with this method and to ensure that they were able to maintain a knee angle of 45 degrees.

A twitch interpolation technique was used to ensure a maximum voluntary quadriceps contraction,[124] standardised encouragement was used and patients were prevented from seeing the screen of the system's computer to reduce extraneous influences on maximal isometric contraction. Patients performed three maximum contractions each of 10 seconds' duration with a 1-minute rest between each contraction. The peak of the three extension torques was used for subsequent analysis.

Dynamic balance
The ability to maintain postural stability under dynamic conditions is an important component of

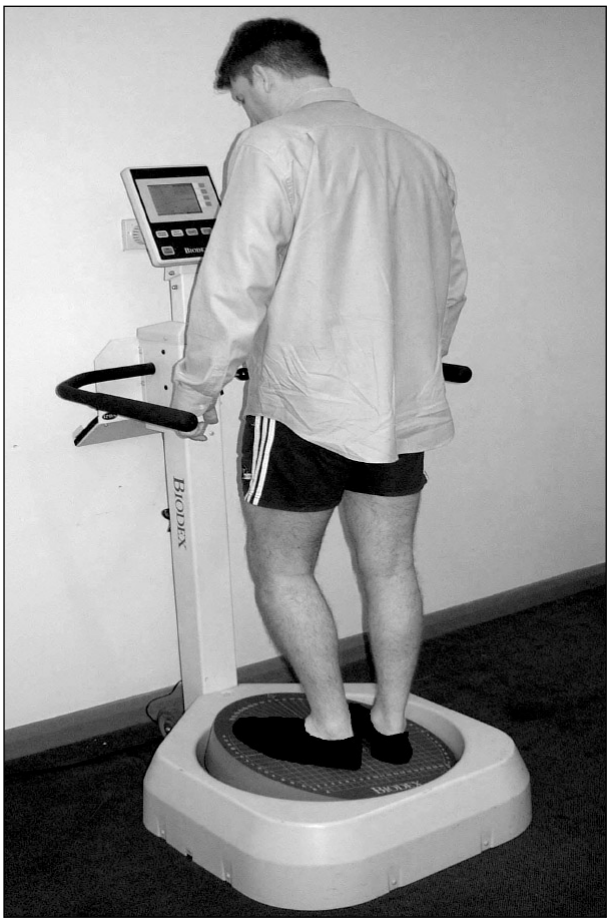

FIGURE 1 *The Biodex stability system*

physical functioning and is achieved through "effective integration of visual, vestibular and proprioceptive neural input to the central nervous system".[125] Decreases in dynamic postural stability have been shown to correlate to an increased risk of falling.[126] One device capable of quantifying postural stability measurements during movement of the base of support is the Biodex stability system (Biodex, Shirley, NY, USA). This device has a platform that can tilt 20 degrees in any direction and can be used to measure overall stability and stability in the anteroposterior (AP, *Ay*) and mediolateral (ML, *Ax*) directions (*Figure 1*). The relative stability (resistance to deflection) of the platform can be altered to suit the postural stability of the test subject, thus enabling safe testing of young to elderly patients.

Previous investigators have reported good test–retest reliability of the Biodex stability system ($ICC_{1,1}$ from 0.71 to 0.95)[125,127] and established that the system has a learning effect necessitating the performance of two training test repetitions before data are collected to ensure instrument familiarity in the subject.[128]

Procedure

Patients were instructed to stand on the platform of the stability system. Footwear was worn and the patients were instructed to flex their knees by 10 degrees. During all tests, patients stood with their feet 15 cm apart and with 20 degrees of forefoot abduction.[129] The patient was then instructed to keep a cursor in the middle of a target by actively maintaining their balanced position. Platform deflection was set at 8, the most stable setting, throughout the testing duration. After two 20-second practice tests the patient undertook three 20-second tests. Platform deflection data from the test were sampled at 20 Hz and converted into stability indices for the *Ay* and *Ax* directions by the system's in built software. The mean of the three test results, for *Ax* and *Ay*, was calculated and used for subsequent analysis.

Range of movement (knee flexion)

Patients with knee osteoarthritis have been shown to have reduced range of knee flexion[45] compared with age-matched healthy people, and increasing range of movement is a common aim of physiotherapeutic treatment.[35] Reduced knee flexion has been shown to be the strongest correlate of disability of all the movements of the knee and hip,[127] and thus was chosen as the movement for assessment. Range of active movement is measured clinically by goniometry.[130] Goniometric measurement of knee range of movement has been shown to be more accurate and reliable than visual estimation alone.[131] The measurement of active flexion of the knee has been shown to have high intratester reliability (ICC = 0.98) and high criterion-related validity (r = 0.87) compared with X-ray-determined angles of flexion of the knee.[131,132]

Procedure

The procedure adopted for the measurement of active knee flexion was that adopted by Messier.[45] With the knee extended and the patient supine, knee flexion was measured by instructing the patient to bring the heel as close as possible to the buttock while the foot remained in contact with the treatment plinth. A universal goniometer was placed on the lateral aspect of the knee, with one arm in line with the lateral malleolus and the other in line with the greater trochanter of the femur. From this position the knee was extended maximally with the foot still in contact with the treatment plinth and any lack of full extension measured using the goniometer, placed in the same position. The mean of three test repetitions was recorded for use in subsequent analysis, as this

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

procedure has been shown to increase intertest reliability coefficients.[131]

Compliance with home exercise

Non-compliance has been defined as "a failure by patients to follow advice",[133] and non-compliance with physiotherapy regimens in the treatment of knee osteoarthritis is well documented.[133,134] Low levels of mobility, muscle weakness and high levels of co-morbidity have been identified as factors associated with high non-compliance with exercise.[135] In patients with knee osteoarthritis poor compliance with class-based exercise regimes has been positively correlated with duration of pain before commencement of exercise and pain scores,[134] with issues of expectation of benefit having a large influence on compliance.[133]

Procedure

Unfortunately, there is no gold standard for measuring compliance as compliance needs to be defined situationally.[136] To assess compliance with the home exercise programme patients were required to complete a compliance questionnaire at their 6- and 12-month post-treatment assessments (see Appendix 1). The questionnaire asked the patients to detail how many times they had performed the home exercises in the past week, how long they spent doing the exercises, whether they had stopped doing the exercises and if so when. In addition, the patients were asked whether they felt that their physical activity levels had gone up, stayed the same or gone down in the previous 6-month period.

Reliability of physical outcome measures

To establish population-specific intra-rater reliability data, a replication design reliability study[137] was conducted with the trial's pilot study group. The study's pilot group undertook a pretreatment test–retest reliability study for the functional measures that were being considered for aggregation into one locomotion functional score, namely, walking time, stairs, and timed up and go. The pilot study also investigated the reliability of the range of flexion measure and the AP and ML body-sway measures.

Pilot study patients (n = 15) attended for pretreatment assessment and then repeated a replicate assessment within 1 week. Data from these two assessments were then analysed for intra-rater, test–retest reliability. To calculate useful indices of reliability four statistics were calculated: ICC with 95% confidence intervals (CI), standard errors of measurement (SEMs) and smallest detectable differences (SDDs). To assess for bias between the visits that may suggest an improvement in locomotor function due to an inherent learning effect, the 95% limits of agreement for the ALF were also plotted (*Figure 2*).

Results

The results of the pilot study test–retest reliability results are shown in *Table 2*. Excellent reliability was demonstrated for each of the locomotor function scores and also for the ALF score. The lowest individual SEM and SDD values were

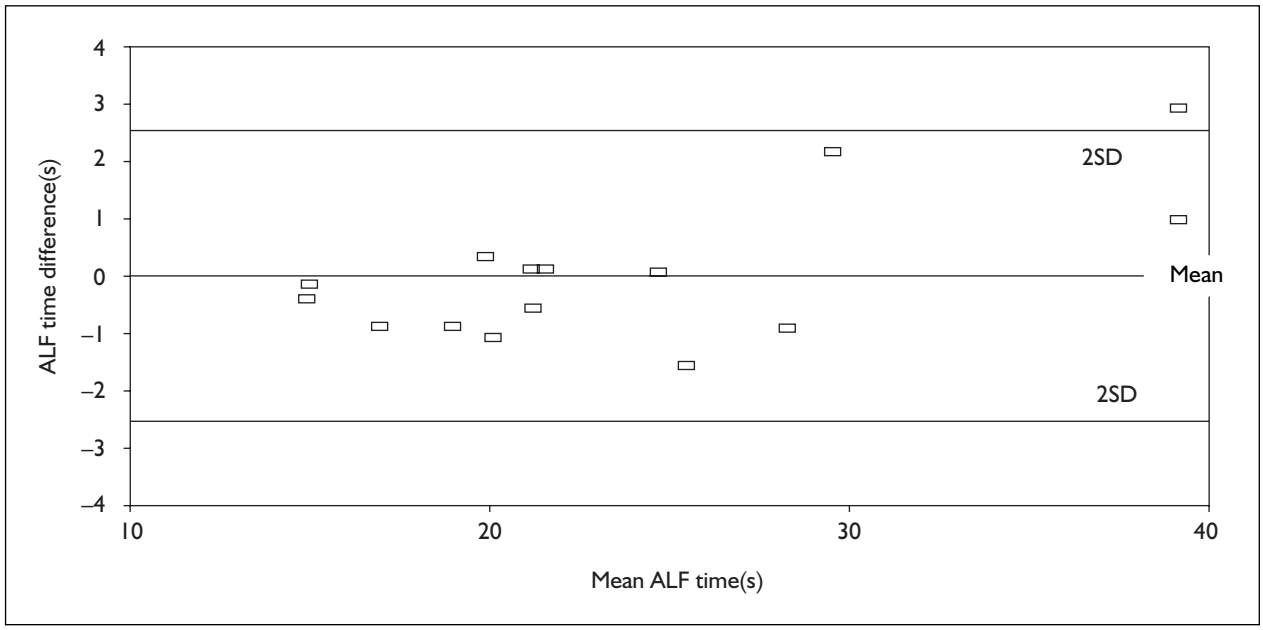

FIGURE 2 *Plot of 95% limits of agreement for the ALF score. The difference in means and distribution of differences between the two tests are shown, with lines representing the mean difference with 2 SD above and below it.*

TABLE 2 *Pilot study reliability indices (n = 15)*

	$ICC_{1,k}$	95% CI	SEM	SDD (%)
Walk time	0.98	0.97 to 0.99	0.26 (s)	18.4
Stair time	0.98	0.94 to 0.99	0.87 (s)	30.6
Up and go	0.99	0.96 to 0.99	0.38 (s)	22.7
ALF	0.99	0.98 to 0.99	0.86 (s)	9.5
Range of flexion	0.78	0.62 to 0.86	1.32°	1.1
Isometric strength	0.99	0.89 to 0.99	3.95 (Nm)	8.4
AP stability	0.90	0.91 to 0.97	1.19	68
ML stability	0.90	0.83 to 0.94	1.30	95

All values $p < 0.01$.

demonstrated by the walk time score, with the highest values being demonstrated by the stair time score. The ALF demonstrated an extremely low SDD score with narrow confidence intervals and a high ICC statistic. Good reliability was also demonstrated for AP and ML sway, isometric muscle strength and range of knee flexion. All values were statistically significant ($p < 0.01$). There was no systematic improvement or bias between the two visits for the ALF score (*Figure 2*), negating the likelihood of an inherent learning effect for these measures.

Participant flow and follow-up

Patients were referred to the trial from the sources detailed earlier in this chapter (section 'Subjects', p. 5). Following interview and consenting procedures, the patients were randomly allocated to either the full or the core assessment group. The process of allocating patients to the full or core assessment group was undertaken to reduce the number of assessments required by the majority of the patients. Reducing contact time with the lead investigator was seen as a way of reducing the testing effect threats to the internal and external validity of the trial.[138] Core assessment lasted for approximately 30 minutes and full assessment involved an assessment time of approximately 60 minutes. In addition, by reducing the number of visits required for assessments it was envisaged that patients would be less inconvenienced and thus the dropout rate would be reduced. The allocation process involved using sealed envelopes containing computer-generated random allocation slips that were opened at the patient's initial attendance. Patients allocated to the core assessment group undertook only core outcome measures before and after treatment assessments, whereas the full assessment group undertook both core and full outcome measures.

Core outcomes:

- VAS pain
- 8-m walk
- sit/stand transferring
- stair ascent and descent
- WOMAC questionnaire
- SF-36/EuroQol questionnaires
- range of movement.

Full outcomes: patients allocated to the full assessment group undertook the measures listed above but also undertook measures of:

- dynamic standing balance
- muscle strength.

All patients were then allocated to one of the two treatment arms of the trial using the process detailed earlier (section 'Assignment', p. 7) and, following an initial advice and assessment session, conducted by the treating physiotherapist, undertook one of the two treatment interventions. At follow-up at 6 and 12 months the patients were reassessed and exercise compliance data were collected. In addition, data regarding service usage were collected at 3-monthly intervals during the 12-month follow-up period (*Figure 3*).

Intervention

Advice and education

Educational advice is considered essential by the ACR, the BSR, the RCP and the SCICSTTT[23–25] in the conservative management of knee osteoarthritis. Educational components are included as standard in knee osteoarthritis treatment programmes provided by physiotherapists[14] (see section 'Patient education programmes', p. 3).

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

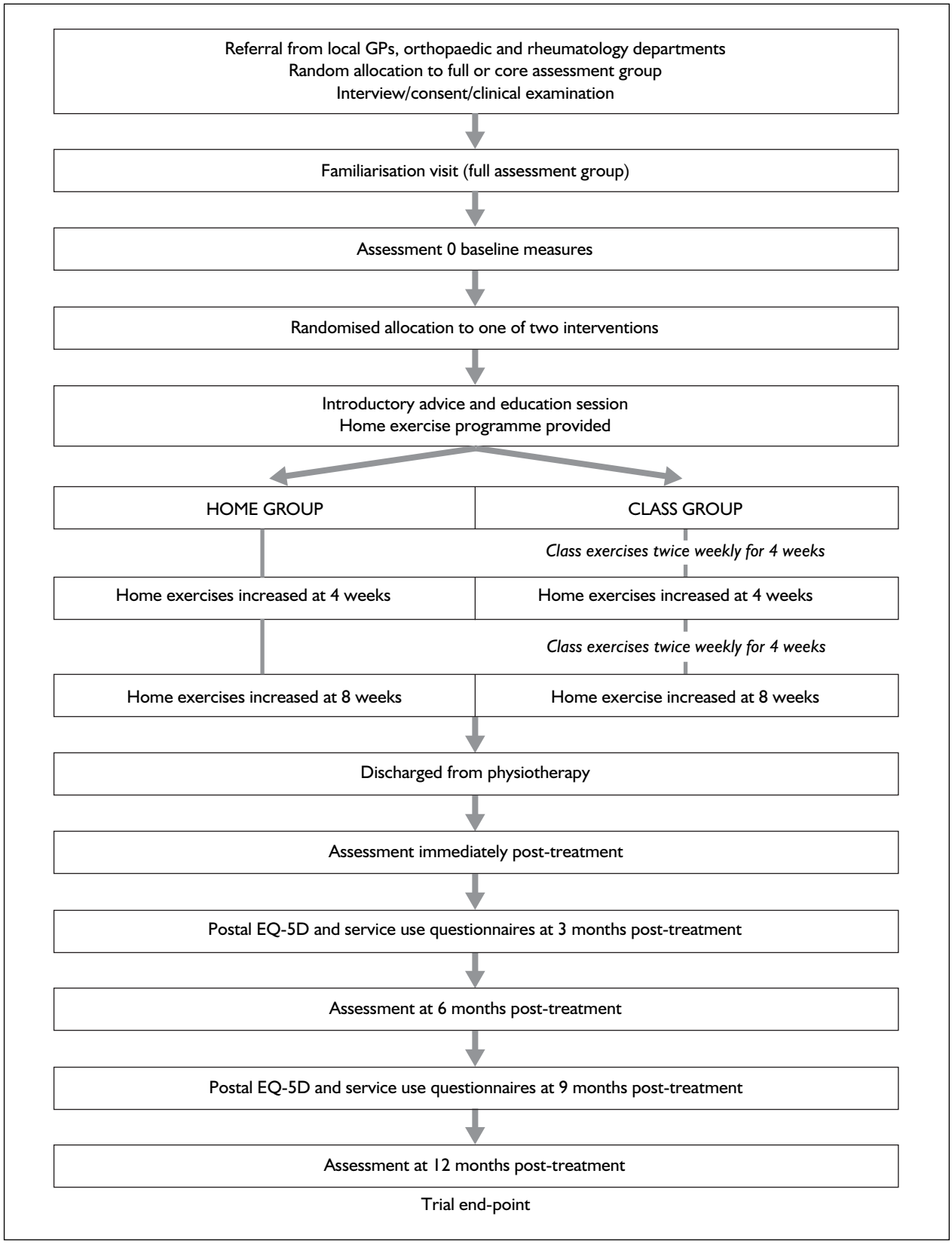

FIGURE 3 *Participant flow*

The advice and education provided consisted of an initial session attended by patients allocated to either treatment arm of the trial. Following this initial session no further advice or education was provided for either group, to try to ensure equivalence between groups. The advice and education presented was drawn from the Arthritis Research Campaign's information booklet "Osteoarthritis of the knee",[39] to present information that was nationally available to patients and physiotherapists, thus increasing the external validity of this element of the trial. The features of the advice and educational information presented are shown in Appendix 2.

Home exercise programme

Following the presentation of advice and educational information the patients were assessed by the treating physiotherapist, to establish the intensity of exercise that each patient should undertake at home.

Exercise programme components

The exercise programme was developed by selecting elements from the programmes used by several recent authors.[3,37,57,59,139] These trials have subsequently been shown to have acceptable validity in a systematic review of the effectiveness of exercise in the treatment of knee osteoarthritis.[60] The exercise intervention was designed to include multiple components that would address the individual features of dysfunction associated with knee osteoarthritis and collectively improve the functional capacity and pain of the patients. The main areas of dysfunction addressed were muscle weakness, muscle fatigue, reduced locomotor function and reduced balance. The exercise programme was designed to address recommended goals of treatment:[140]

- reduction of impairment and improvement of function
- protection of the joint by reducing stress on the joint, attenuating joint forces and improving biomechanics
- prevention of disability and poor health secondary to inactivity by increasing daily physical activity.

Muscle weakness was addressed by including muscle strengthening exercises.

- Sitting to standing: this exercise involved the patient rising from sitting to standing and then lowering themselves gently back to the chair seat. This exercise was repeated to a number of repetitions. The number of repetitions was determined at initial assessment.
- While standing, the patient contracted the quadriceps femoris muscle group maximally and held the contraction for a period determined at initial assessment.
- While sitting, the patient extended the knee from 90 degrees of flexion to the maximum degree of extension they could obtain and held the leg in this position for 10 seconds. The knee was then slowly flexed to 90 degrees. The number of repetitions was determined at assessment.

Muscle fatigue was addressed by the performance of a muscular endurance exercise. This involved the patient rising from a seated position to a position of approximately 45 degrees of knee flexion. The patients then held that position by maintaining isometric tension in the lower limb extensors for a period determined at initial assessment.

Range of movement increase was addressed by the performance of three stretches.

- An anterior thigh and hip stretch was obtained by gentle translation of the pelvis anteriorly, while standing. This manoeuvre stretches the anterior thigh, rectus femoris muscle and hip of the posteriorly placed leg, while also stretching the calves and ankles.
- A posterior calf stretch was obtained by gently flexing the knees while standing, ensuring that the heels remained in contact with the floor.
- A posterior stretch of the knee was obtained by contracting the quadriceps femoris group while standing, thus generating an extension moment to place tension on the posterior knee musculature, joint capsule and ligaments.

Standing balance was addressed by patient standing on one leg (close to a supporting surface), thereby placing themselves in a situation requiring increased conscious balance control and integration.[141] The number of times that balance was lost was recorded by patients while they performed the exercise for 2 minutes.

The exercise sheet given to patients is shown in Appendix 3.

Exercise assessment/reassessment

To facilitate maximum improvement the intensity of exercise programmes should be individualised to the patient[142] and to achieve this the exercise programme was based on assessment and

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

reassessment procedures. At initial assessment the treating physiotherapist collected the following data:

- the number of sit to stand repetitions that could be performed in 1 minute
- the length of time for which a quadriceps femoris contraction could be held while standing
- the length of time for which a contraction could be held with the knee flexed to 45 degrees.

These values were considered to represent baseline exercise ability. Sixty per cent values were calculated and given to patients as their individualised targets for home exercise. Four weeks after initial assessment, patients were reassessed by the same method. These data were then used to calculate 70% values, which were then given to patients as their individualised targets for the next 4 weeks. Four weeks after their second assessment the patients were reassessed for the final time and data from this visit were used to calculate 80% values. These values formed the patient's targets for the home exercise programme, which they were to continue indefinitely.

Class exercise programme

As well as undertaking the home exercise programme detailed above, the patients allocated to the class programme undertook the exercise intervention detailed below. The class exercise programme involved attendance at a physiotherapy department twice weekly with classes lasting for approximately 45 minutes. During the classes the patients undertook a circuit of exercises supervised by a senior physiotherapist. Classes were small, with a maximum of 12 patients in each class.

The exercise circuit that was performed was as follows:

- a warm-up period using a 'shuttle walking test' or 'Bleep test' tape,[143] which encouraged the patients to accelerate gradually while walking for 5 minutes
- muscle stretching for 5 minutes
- balance training using balance boards (Procare Medisport, Oldham, Lancashire, UK) for 5 minutes
- isotonic, functional, weight-bearing exercises (e.g. step-ups and sit to stands) for 10 minutes
- isometric quadriceps exercises performed at 45 degrees of knee flexion, using a handheld myometer (Campden Instruments, Leicestershire, UK) for 5 minutes
- a cool-down period of gentle walking and stretching for 5 minutes.

Progression and regression of exercise

The home exercise programme was progressed as detailed above (exercise assessment/reassessment). In the event of an exacerbation of symptoms the home programme was reduced to original 60% values for a week and then returned to previous levels. If the exacerbation was severe, exercise was suspended for 1–2 weeks to allow natural resolution of symptoms. Exercise was then returned to 60% values for a week, then returned to the levels before the exacerbation. The class-based exercise programme was increased and decreased by the senior physiotherapist using clinical discretion and in discussion with the patient.

Analysis of clinical effectiveness

The primary outcome in this trial was the ALF. Secondary outcomes were VAS pain, WOMAC, SF-36, strength, balance and compliance with home exercise.

Data were recorded at baseline before randomisation, post-treatment, and at 6 and 12 months' follow-up. The main statistical analysis comparing the two therapies was based on a general linear mixed model analysis of covariance applied to longitudinal data in which a variance term is fitted to account for within-subject correlation.[144] The analysis was carried out using Stata Release 7 (Stata Statistical Software StataCorp, Texas, USA, 2001). For each outcome the model was fitted to the outcome across the three post-treatment time-points including BMI, age, gender, core or full outcome group and the prerandomisation values as covariates. Normal probability plots were used to check distributional assumptions of the model. For some outcomes there was evidence of skewness. There was also a ceiling and floor effect in outcomes based on questionnaires, e.g. EQ-5D and WOMAC, particularly those dimensions based on a limited number of questionnaire items. To check whether such violations of distributional assumptions affected the conclusion, confidence intervals were also computed using a non-parametric bootstrap.

Standardised response means (SRMs) were calculated by taking the adjusted difference between the change scores of the intervention groups and dividing it by the pooled standard

deviation of the change score. An SRM size of 0.2 was regarded as small, 0.5 as medium and 0.8 as large.[145]

In a randomised trial such as this, there are inevitably some missing outcome data. Since this may bias the estimate of the treatment effect, the relationship between missing data and outcome was investigated. Logistic regression was used to investigate the predictors of loss to follow-up. Variables that were found to predict loss to follow-up were included as covariates in the statistical model to reduce bias.[145] An ITT analysis on the primary outcome's 12-month data was conducted using last value carried forward (LVCF) imputation to examine further the effect of missing data.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Chapter 3
Results

Participant flow

A flowchart detailing the flow of participants through each stage of the trial is presented in *Figure 4*. Following the Consolidating Standards of Reporting Trials (CONSORT) guidelines, this figure shows specifically for each group the numbers of participants randomly assigned, receiving treatment, completing the study protocol and analysed for primary outcomes.[146] Over the 20-month recruitment period 302 referrals to the trial were received. Despite a second appointment being sent out to patients, 62 (21%) patients did not attend for assessment. Of the 240 patients who attended for assessment 225 gave their written consent and were subsequently enrolled onto the trial. Of the 225 patients who consented to join the trial 214 were allocated to treatment after 11 patients withdrew from the trial before allocation. These patients had been considered suitable for exercise by their referring physician, but withdrew owing to personal concerns regarding comorbidity. Of the 214 patients allocated into the two groups, 190 (89%) patients attended for post-treatment assessment. The loss to review at this point consisted of 17 patients from the home treatment group and seven patients from the class group. At 6-month review 182 (85% of allocated patients) attended for reassessment, with a total of 24 patients being lost from the home group and eight patients from the class group. At 12 months 151 (71% of allocated patients) attended for assessment, with 32 being lost from the home group and 31 from the class group. The predominant reason for non-attendance was that the patients did not want to attend for review because they had stopped doing their home exercises (n = 17 home group, n = 15 class group). The second biggest cause of loss to follow-up was patients being no longer included in the trial following recent injection or surgical treatment (n = 12 home group, n = 10 home group).

Baseline characteristics of patients

The baseline characteristics of both home and class groups are shown in *Table 3*.

Investigation of loss to follow-up

The pattern of follow-ups was broadly similar for each of the outcomes. *Table 4* shows the distribution of last follow-ups for ALF, WOMAC

TABLE 3 *Baseline characteristics of randomised groups*

	Freq.	Home (%)	*n*	Freq.	Class (%)	*n*
Women	62	(60.2)	103	63	(56.8)	111
Self-instigated Referral	39	(37.9)	103	40	(36.0)	111

	Mean	SD	Min.	Max.	*n*	Mean	SD	Min.	Max.	*n*
Age (years)	64.9	9.7	40.7	81.7	103	64.5	9.9	40.2	86.8	111
BMI	30.2	5.3	18.6	47.7	103	29.4	5.2	17.2	46.1	111
ALF	26.5	11.8	13.2	85.0	102	24.5	11.8	12.8	103.0	111
Flexion	114.7	15.6	45.0	142.0	103	117.9	14.5	70.0	145.0	111
VAS pain	62.3	18.6	10	100	103	63.3	17.4	17	100	110
WOMAC total	45.3	18.9	9	85	91[a]	45.3	18.2	6	96	100[a]
Pain	10.0	3.7	2	19	97[a]	9.6	3.7	1	20	106[a]
Stiffness	4.5	1.7	1	8	97[a]	4.2	1.8	0	8	108[a]
Physical function	30.8	14.4	4	63	91[a]	29.6	13.7	2	68	102[a]

[a] Smaller data set due to incomplete or incorrect completion of the WOMAC questionnaire.
Freq., frequency.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

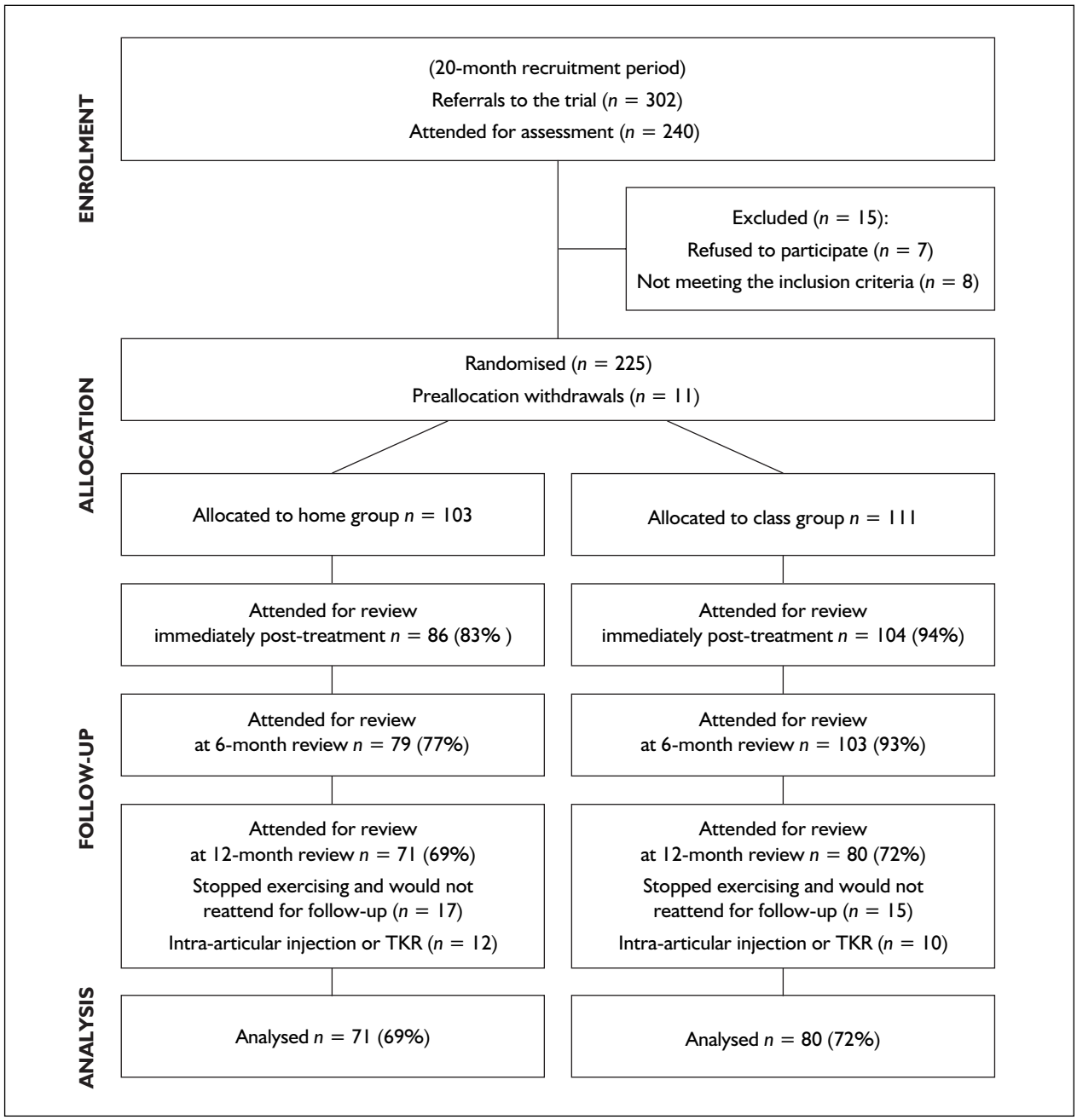

FIGURE 4 *CONSORT diagram showing participant flow through the trial*

TABLE 4 *Follow-up for ALF, VAS, WOMAC and SF-36 physical function (PF) scales*

Follow-up	ALF		VAS		WOMAC		SF-36 (PF)	
	Home	Class	Home	Class	Home	Class	Home	Class
Post-treatment	86 (83%)	102 (92%)	90 (87%)	105 (95%)	79 (77%)	93 (84%)	82 (80%)	100 (90%)
6 months	79 (77%)	103 (93%)	81 (79%)	103 (93%)	76 (74%)	95 (86%)	75 (73%)	96 (86%)
12 months	71 (69%)	80 (72%)	78 (76%)	90 (81%)	62 (60%)	76 (68%)	65 (63%)	79 (71%)
No. randomised	103	111	103	111	103	111	103	111

and VAS scores, and SF-36 physical function dimensions.

The follow-up was greater in the class group than the home exercise programme group. For the ALF at post-treatment 92% were followed up in the class group compared with 83% in the home programme group. At 6 months, follow-up in the class group (93%) was substantially better than for the home programme group (77%). This became less marked at 12 months with the loss to follow-up being similar for each group (72–69%).

The pattern of follow-ups was broadly similar for each of the outcomes. Loss to follow-up was of a magnitude reported by previous authors in this field.[31] Logistic regression analysis of loss to follow-up at the three time-points confirmed that patients in the class group were more likely to respond at post-treatment and 6 months, but not at 12 months; however, baseline patient characteristics did not appear to affect response. For the trial's primary outcome measure (the ALF score), the odds ratio of an outcome being recorded in the class group compared with the home exercise group was 2.3 (95% CI 0.94 to 5.4, $p = 0.067$) at post-treatment and 3.9 (95% CI 1.67 to 9.3, $p = 0.002$) at 6 months. At 12 months loss to follow-up was no longer associated with treatment group (odds ratio = 1.1, 95% CI 0.6 to 0.20, $p = 0.728$).

In a secondary analysis, patients who attended for review only up to 6 months post-treatment appeared to have poorer locomotor function, regardless of treatment, than those with complete follow-up (ALF scores for incomplete follow-up were increased by 1.93 seconds, 95% CI 0.34 to 3.52, $p = 0.018$). When an interaction term was fitted to the model, the treatment effect nevertheless appeared to be similar between patients with only post-treatment follow-up and those with up to 6 months and complete follow-up data ($p = 0.345$).

Comparison of outcomes for home and class exercise groups

ALF score

Statistical analysis tested for any difference in the treatment effect according to length of follow-up (post-treatment, 6 months or 12 months post-treatment) by adding a time–treatment interaction term to the statistical model. For the ALF score a likelihood ratio test did not suggest an interaction ($p = 0.671$). In the absence of an interaction it was appropriate to examine the pooled treatment effect across the three time-points. The pooled estimate of treatment effect of class compared with home exercise programmes is highlighted in *Table 5*. For the ALF score there was a reduction in the score of –2.89 seconds (95% CI –1.82 to –3.96, $p < 0.001$) after adjustment for baseline values, BMI, age and gender. A cross-sectional analysis is given for each of the three follow-up points, giving the effect of treatment adjusted for baseline ALF, BMI, age and gender. Comparing the adjusted

TABLE 5 *Comparison of home and class groups for ALF score*

ALF (seconds)	Home		Class		Mean diff.[a]	95% CI[b]	SRM	*p*
	Mean	(SD)	Mean	(SD)				
Baseline	26.5	(14.8)	24.5	(13.2)				
Post-treatment	24.4	(10.8)	18.7	(5.9)	–3.45	(–4.46 to –2.44) *(–4.39 to –2.47)*	0.40	<0.001
6 months	25.4	(11.2)	20.6	(10.8)	–2.56	(–3.81 to –1.31) *(–3.89 to –1.39)*	0.23	<0.001
12 months	24.8	(9.7)	19.1	(5.4)	–3.68	(–4.87 to –2.50) *(–4.81 to –2.58)*	0.47	<0.001
12-month LVCF	25.6	(10.2)	20.9	(10.7)	–2.70	(–3.82 to –1.58)	0.26	<0.001
Interaction								0.671
Pooled estimate					–2.89	(–3.96 to –1.82)		<0.001

[a] Estimated treatment effect adjusted for BMI, age, gender and baseline values.
[b] Negative values for mean differences reflect improvement. Bootstrap confidence intervals in italics.
diff., difference; 12-month LVCF, ITT analysis using last value carried forward imputation.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

TABLE 6 *Comparison of home and class groups for VAS pain score*

VAS (mm)	Home		Class		Mean diff.[a]	95% CI[b]	SRM	*p*
	Mean	(SD)	Mean	(SD)				
Baseline	62.3	(18.6)	63.3	(17.4)				
Post-treatment	54.8	(18.9)	37.3	(16.9)	–18.1	(–21.8 to –14.4) *(–21.7 to –14.4)*	1.01	<0.001
6 months	54.6	(21.8)	43.0	(18.1)	–11.4	(–15.6 to –7.10) *(–15.5 to –7.25)*	0.57	<0.001
12 months	59.1	(18.2)	43.6	(18.1)	–15.2	(–19.5 to –10.9) *(–19.6 to –11.1)*	0.84	<0.001
Interaction								0.004
Pooled estimate					–14.9	(–18.1 to –11.7)		<0.001

[a] Estimated treatment effect adjusted for BMI, age, gender and baseline values.
[b] Negative values for mean differences reflect improvement. Bootstrap confidence intervals in italics.

class treatment with the home group suggests that the reduction in ALF scores was 14%, 11% and 15% greater in the supplemented group, at post-treatment, 6-month and 12-month reviews. Small-sized SRMs were evident at all follow-ups.

A more conservative statistical approach to examining the issue of missing data was also undertaken by calculating the ITT analysis values for the trial's primary outcome measure at 12-month follow up. Using the LVCF method of imputing missing data, a slightly smaller treatment effect was observed (–2.70 seconds, 95% CI –3.82 to –1.58). To examine the possibility of floor and ceiling effects of the instrument the bootstrap 95% confidence intervals were also calculated and are presented in *Table 5*. The limits of these intervals are not significantly different to the original limits, suggesting no significant influence of these effects.

VAS score

For the VAS score there was evidence of a difference in treatment effect between time-points, with a time–treatment interaction term that was statistically significant ($p = 0.004$). A cross-sectional analysis is presented in *Table 6*. There was evidence of both a difference in treatment effect between time-points and a substantial improvement in the VAS at all follow-ups. Comparing the adjusted class treatment with the home group suggests that the reduction in VAS scores was 33%, 21% and 25% greater in the supplemented group, at post-treatment, 6 months and 12 months, representing moderate to large SRMs.

To examine the possibility of floor and ceiling effects of the instrument the bootstrap 95% confidence intervals were also calculated and are presented in *Table 6*. The limits of these intervals are not significantly different to the original limits, suggesting no significant influence of these effects.

WOMAC score

Likelihood ratio tests did not suggest time–treatment interactions for the three WOMAC domain scores. In the absence of an interaction it was appropriate to examine the pooled treatment effects across the three time-points. The pooled estimates of treatment effect of class compared with home exercise programmes are detailed in *Table 7*. For the WOMAC pain domain there was a reduction in score of –1.18 (95% CI –1.85 to –0.52), stiffness domain of –0.46 (95% CI –0.81 to –0.12) and physical function domain of –3.39 (95% CI –5.58 to –1.20) after adjustment for baseline values, BMI, age and gender. There was no significant treatment effect in physical function or stiffness domains at 6-month follow-up, probably owing to the higher dropout rate at this time-point. Overall, the pooled treatment effects represented small SRMs.

To examine the possibility of floor and ceiling effects of the instrument the bootstrap 95% confidence intervals were also calculated and are presented in *Table 7*. The limits of these intervals are not significantly different to the original limits, suggesting no significant influence of these effects.

TABLE 7 *Comparison of home and class groups for WOMAC domain scores*

	Home		Class		Mean diff.[a]	95% CI[b]	SRM	*p*
	Mean	**(SD)**	**Mean**	**(SD)**				
Pain								
Baseline	9.99	(3.71)	9.63	(3.69)				
Post-treatment	9.04	(3.84)	7.50	(3.95)	–1.23	(–2.03 to –1.46) *(–2.04 to –0.44)*	0.32	0.006
6 months	9.13	(3.99)	8.04	(3.60)	–0.84	(–1.70 to –0.14) *(–1.69 to –0.01)*	0.27	0.041
12 months	9.38	(3.53)	8.05	(3.81)	–1.32	(–2.33 to –0.35) *(–2.34 to –0.34)*	0.36	0.036
Interaction								0.752
Pooled estimate					–1.18	(–1.85 to –0.52)		0.001
Stiffness								
Baseline	4.53	(1.68)	4.18	(1.81)				
Post-treatment	4.19	(1.84)	3.36	(1.93)	–0.53	(–0.97 to –0.09) *(–0.96 to –0.09)*	0.28	0.019
6 months	4.09	(1.77)	3.37	(1.78)	–0.41	(–0.85 to 0.03) *(–0.83 to 0.02)*	0.23	0.068
12 months	3.97	(1.59)	3.36	(1.81)	–0.39	(–0.89 to 0.11) *(–0.87 to 0.11)*	0.23	0.129
Interaction								0.814
Pooled estimate					–0.46	(–0.81 to –0.12)		0.009
Physical function								
Baseline	30.8	(14.4)	29.6	(13.7)				
Post-treatment	28.1	(14.7)	23.6	(13.9)	–3.19	(–5.84 to –0.09) *(–5.87 to –0.57)*	0.22	0.018
6 months	29.8	(14.5)	26.6	(14.2)	–2.37	(–4.86 to 0.03) *(–4.84 to 0.09)*	0.17	0.062
12 months	30.7	(16.5)	26.5	(13.6)	–5.00	(–8.97 to –0.10) *(–9.47 to –1.27)*	0.33	0.014
Interaction								0.504
Pooled estimate					–3.39	(–5.58 to –1.20)		0.003

[a] Estimated treatment effect adjusted for BMI, age, gender and baseline values.
[b] Negative values reflect improvement. Bootstrap confidence intervals in italics.

SF-36 score

Only two of the SF-36 dimensions demonstrated a statistically significant treatment effect: the pain and physical function dimensions demonstrated small but statistically significant pooled treatment effects of 7.39 (95% CI 3.43 to 11.34) and 5.61 (95% CI 169 to 9.52), respectively (*Table 8* and *Figure 5*).

EuroQol score

EQ-5D scores are presented in Chapter 4 (section 'Health states and their value', p. 31) however, health status as measured by the EuroQol VAS instrument is presented here in detail. Statistical analysis tested for any difference in the treatment effect according to length of follow-up (post-treatment, 6 months or 12 months post-treatment) by adding a time–treatment interaction term to the statistical model. For the EuroQol VAS score a likelihood ratio test did not suggest an interaction ($p = 0.671$). In the absence of an interaction it was appropriate to examine the pooled treatment effect across the three time-points. The pooled estimate of treatment effect of class compared with home exercise programmes is shown in *Table 9*. For the EuroQol health status VAS score there was

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

TABLE 8 *SF-36 scores*

	Home			Class			Mean diff.[a]	95% CI	*p*
	Mean	**(SD)**	***n***	**Mean**	**(SD)**	***n***			
PF									
Baseline	35.5	(22.9)	97	37.5	(23.4)	109			
Post-treatment	39.4	(22.5)	82	47.9	(23.2)	100	7.14	(2.26 to 12.01)	0.004
6 months	36.7	(23.3)	75	44.6	(24.3)	96	7.18	(1.86 to 12.49)	0.008
12 months	38.4	(22.9)	65	41.1	(23.8)	79	2.96	(–3.11 to 9.03)	0.336
Interaction[b]									0.222
Pooled estimate							5.61	(1.69 to 9.52)	0.005
RLP									
Baseline	30.3	(37.3)	96	32.1	(40.8)	109			
Post-treatment	35.7	(39.7)	82	42.6	(42.0)	98	2.16	(–7.70 to 12.02)	0.666
6 months	41.3	(43.0)	75	40.6	(43.4)	96	–5.15	(–16.85 to 6.56)	0.387
12 months	31.5	(41.0)	65	38.6	(38.3)	78	5.34	(–6.37 to 17.06)	0.369
Interaction[b]									0.410
Pooled estimate							1.01	(–6.62 to 8.64)	0.796
RLM									
Baseline	56.8	(46.3)	95	50.2	(44.6)	109			
Post-treatment	56.8	(44.9)	81	58.1	(43.9)	101	3.66	(–7.23 to 14.55)	0.508
6 months	55.9	(46.5)	74	50.7	(44.2)	94	–3.06	(–15.27 to 9.15)	0.621
12 months	50.0	(45.6)	64	48.3	(44.2)	79	1.56	(–12.19 to 15.32)	0.823
Interaction[b]									0.578
Pooled estimate							1.66	(–7.11 to 10.42)	0.711
SF									
Baseline	62.7	(28.8)	98	64.8	(25.5)	109			
Post-treatment	70.1	(24.2)	83	68.9	(25.9)	102	–3.74	(–8.71 to 1.24)	0.140
6 months	66.2	(25.9)	76	68.4	(21.5)	96	–0.65	(–6.32 to 5.02)	0.822
12 months	64.8	(22.8)	65	69.3	(24.2)	80	2.72	(–3.80 to 9.24)	0.410
Interaction[b]									0.353
Pooled estimate							–1.01	(–5.13 to 3.11)	0.631
MH									
Baseline	67.6	(18.9)	97	63.3	(19.4)	109			
Post-treatment	68.7	(17.8)	82	66.1	(17.9)	100	–0.50	(–4.29 to 3.29)	0.796
6 months	63.4	(20.2)	76	64.4	(16.1)	95	3.48	(–1.06 to 8.01)	0.132
12 months	61.2	(17.5)	64	63.4	(17.4)	79	4.24	(–0.52 to 9.01)	0.081
Interaction[b]									0.136
Pooled estimate							2.02	(–1.10 to 5.15)	0.206
P									
Baseline	40.5	(22.5)	98	41.3	(20.2)	109			
Post-treatment	43.9	(22.2)	82	53.9	(20.7)	101	9.67	(4.85 to 14.49)	<0.001
6 months	44.6	(25.7)	76	50.5	(21.5)	94	5.22	(–0.70 to 11.14)	0.083
12 months	41.5	(19.2)	65	49.7	(18.5)	80	8.12	(2.84 to 13.39)	0.003
Interaction[b]									0.293
Pooled estimate							7.39	(3.43 to 11.34)	0.000
EV									
Baseline	46.5	(20.1)	97	46.7	(19.2)	109			
Post-treatment	50.9	(16.8)	82	51.3	(17.9)	100	–0.83	(–4.62 to 2.96)	0.665
6 months	48.8	(18.3)	76	54.3	(15.1)	95	4.69	(0.49 to 8.89)	0.029
12 months	52.2	(16.6)	64	52.8	(16.5)	79	1.01	(–3.68 to 5.69)	0.671
Interaction[b]									0.063
Pooled estimate							1.46	(–1.60 to 4.52)	0.350

continued

TABLE 8 *SF-36 scores (cont'd)*

	Home			Class			Mean diff.[a]	95% CI	*p*
	Mean	**(SD)**	***n***	**Mean**	**(SD)**	***n***			
HP									
Baseline	53.4	(24.4)	97	53.8	(21.3)	109			
Post-treatment	58.3	(21.8)	81	59.0	(21.6)	100	–0.42	(–5.15 to 4.31)	0.861
6 months	56.8	(21.6)	76	60.9	(19.5)	94	4.34	(–0.49 to 9.17)	0.078
12 months	56.9	(19.6)	64	55.9	(19.8)	77	–0.84	(–6.33 to 4.65)	0.762
Interaction[b]									0.140
Pooled estimate							0.57	(–3.00 to 4.13)	0.756
CIH									
Baseline	41.1	(22.2)	98	40.6	(19.8)	109			
Post-treatment	50.0	(21.7)	83	51.2	(19.5)	101	0.79	(–4.37 to 5.94)	0.764
6 months	48.4	(21.3)	76	47.2	(16.9)	97	–0.77	(–6.09 to 4.55)	0.775
12 months	45.8	(18.5)	65	45.6	(15.8)	80	–0.17	(–5.34 to 5.00)	0.949
Interaction[b]									0.838
Pooled estimate							–0.18	(–3.84 to 3.48)	0.923

[a] Estimated treatment effect adjusted for age, gender, BMI and source of referral.
[b] Treatment–follow-up interaction.
PF, physical function; RLP, role limitation–physical; RLM, role limitation–mental; SF, social functioning; MH, mental health; P, pain; EV, energy/vitality; HP, health perception; CIH, change in health score.

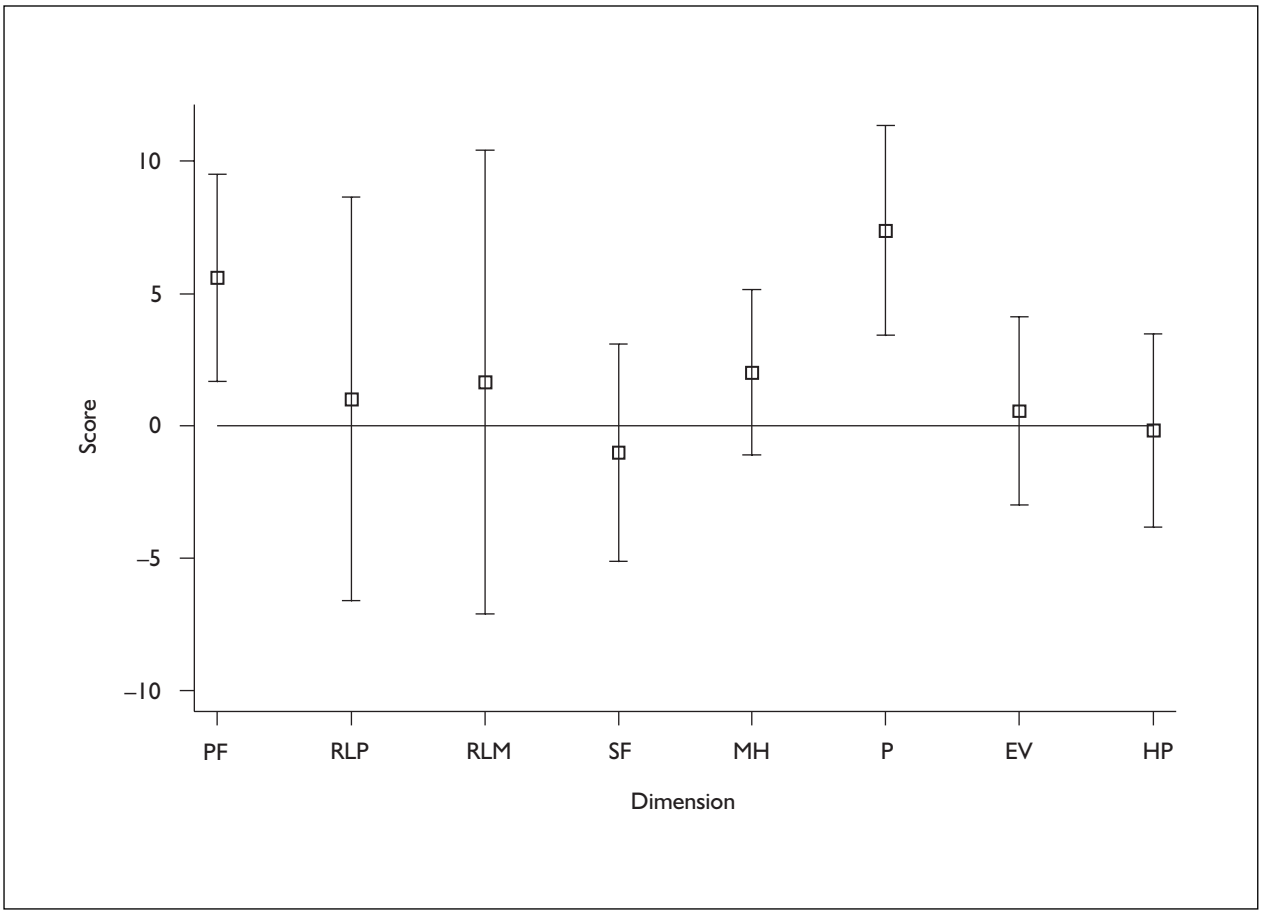

FIGURE 5 *Pooled treatment effects for the SF-36 dimensions. PF, physical function; RLP, role limitation–physical; RLM, role limitation–mental; SF, social functioning; MH, mental health; P, pain; EV, energy/vitality; HP, health perception.*

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

TABLE 9 *EuroQol health VAS thermometer scores*

EuroQol Thermometer (mm)	Home		Class		Mean diff.[a]	95% CI[b]	*p*
	Mean	(SD)	Mean	(SD)			
Baseline	66.7	(18.2)	66.7	(17.7)			
Post-treatment	67.3	(18.1)	69.3	(16.9)	4.3	(–6.5 to 15.2)	0.43
6 months	65.6	(19.9)	67.5	(18.0)	–2.0	(–16.3 to 12.9)	0.79
12 months	66.0	(18.8)	68.4	(16.3)	0.9	(–13.0 to 14.7)	0.91
Interaction							0.97
Pooled estimate					0.4	(–4.2 to 4.9)	0.86

[a] Estimated treatment effect adjusted for BMI, age, gender and baseline values. A positive mean difference represents improvement.

a reduction in the score of 0.4 mm (95% CI –4.2 to 4.9 mm, $p = 0.86$) after adjustment for baseline values, BMI, age and gender. Thus, there was no difference in health status between the groups, or indeed any change in health status within the groups as measured by the EuroQol VAS instrument.

Strength and balance measures

Measures of strength and balance were obtained for only a subsample of subjects (see Chapter 2). The balance measures (AP and ML) and the strength measure (maximum voluntary isometric contraction – MVIC) were positively skewed. A box-Cox transformation suggested a log transformation to remove skewness. All three outcomes were log-transformed. *Table 10* gives the raw arithmetic means for each treatment group and an estimate of the ratio of the geometric means adjusted for age, gender, BMI and source of referral.

There was evidence of improved balance and strength immediately post-treatment. Although the treatment–follow-up interaction term was not statistically significant, the effect of treatment appeared to reduce over time for all three measures. This may be explained by a lack of power in this subsample. Pooled estimates for AP and ML were statistically significant, but it would be inappropriate to conclude that there was a sustained improvement in these to measures at 12 months. Thus, while providing a short-term greater improvement in strength and balance by 6 months, there was significant treatment effect in the supplemented group.

Range of movement (knee flexion)

There was evidence of an effect of treatment on range of movement, but this was reduced at follow-up (*Table 11*). The measurement of flexion has a ceiling of less than 18 degrees for anatomical reasons, resulting in the measure of flexion being negatively skewed. In this sample the maximum across all time-points was 155 degrees. Use of a $\log_e(155 - Y)$ transformation removed this skewness and normalised the residuals of the model. On this scale the results were broadly similar to the non-transformed data. The time–treatment interaction term was statistically significant ($p = 0.007$). The cross-sectional analyses at all three post-treatment time-points were all statistically significant (post-treatment $p < 0.0001$, 6 months $p = 0.023$, 12 months $p = 0.012$). Thus, although statistically significant differences were demonstrated between the groups the size of the difference was small and of the same magnitude as the measurement error expected. As a result it would be inappropriate to conclude that the class group demonstrated a greater improvement in range of movement than the home group.

Compliance with home exercise

There was some suggestion of increased activity in the class group (*Table 12*). Although similar proportions reported no change in each treatment group, a greater proportion reported increased activity in the class group and correspondingly a smaller proportion reported reduced activity. When an ordinal logistic model[147] was fitted, the common odds ratio was 1.82 (95% CI 0.92 to 3.62, $p = 0.09$) at 6 months and 2.07 (95% CI 1.07 to 4.00, $p = 0.03$) at 12 months.

At 6 and 12 months subjects were asked the frequency with which they conducted their home exercise programme and the time they took performing the programme. *Tables 13* and *14*, respectively, show these responses. At 6 months the median response was twice a week for both groups. At 12 months the median response for the

TABLE 10 *Strength and balance scores*

	Home			Class			GMean ratio[a]	95% CI	*p*
	Mean	**(SD)**	***n***	**Mean**	**(SD)**	***n***			
AP Mean									
Baseline	2.13	(1.04)	23	2.15	(0.81)	29			
Post-treatment	1.92	(0.76)	24	1.56	(0.35)	30	0.85	(0.74 to 0.97)	0.017
6 months	1.99	(0.68)	24	1.77	(0.38)	31	0.90	(0.79 to 1.04)	0.146
12 months	1.87	(0.42)	18	1.86	(0.45)	27	1.05	(0.90 to 1.22)	0.551
Interaction[b]									0.389
Pooled estimate							0.90	(0.81 to 0.99)	0.035
ML Mean									
Baseline	1.77	(0.64)	23	1.75	(0.58)	29			
Post-treatment	1.56	(0.56)	24	1.19	(0.30)	30	0.77	(0.67 to 0.88)	0.000
6 months	1.63	(0.54)	24	1.47	(0.39)	31	0.89	(0.78 to 1.02)	0.093
12 months	1.60	(0.36)	18	1.47	(0.32)	27	0.99	(0.86 to 1.13)	0.854
Interaction[b]									0.164
Pooled estimate							0.26	(0.38 to 0.15)	0.001
MVIC									
Baseline	59.9	(25.1)	29	54.9	(24.6)	35			
Post-treatment	59.9	(21.6)	25	71.1	(32.1)	31	1.16	(1.03 to 1.30)	0.014
6 months	63.9	(23.2)	25	68.7	(31.8)	34	1.02	(0.87 to 1.18)	0.828
12 months	65.6	(21.1)	16	70.5	(38.5)	27	0.99	(0.86 to 1.13)	0.854
Interaction[b]									0.085
Pooled estimate							1.06	(0.94 to 1.19)	0.359

[a] Estimated treatment effect as ratio of geometric means adjusted for age, gender, BMI and source of referral on a log scale.
[b] Treatment–follow-up interaction.
MVIC, maximum voluntary isometric contraction.

TABLE 11 *Range of knee flexion*

Flexion	Home			Class			Mean diff.[a]	95% CI	*p*
	Mean	**(SD)**	***n***	**Mean**	**(SD)**	***n***			
Baseline	114.7	(15.6)	103	117.9	(14.5)	111			
Post-treatment	119.0	(13.9)	86	124.9	(12.2)	104	3.7	(2.0 to 5.5)	<0.0005
6 months	119.1	(11.4)	79	121.8	(12.0)	103	1.7	(–0.1 to 3.6)	0.058
12 months	118.5	(11.7)	71	122.1	(11.3)	80	1.7	(0.0 to 3.5)	0.052
Interaction[b]									0.092
Pooled estimate							2.7	(1.2 to 4.2)	0.0005

[a] Estimated treatment effect adjusted for age, gender, BMI and source of referral.
[b] Treatment–follow-up interaction.

TABLE 12 *Activity changes in each treatment group*

	6 months						12 months					
	Home	**(%)**	**Class**	**(%)**	**Total**	**(%)**	**Home**	**(%)**	**Class**	**(%)**	**Total**	**(%)**
Increased	4	(6.5)	12	(14.3)	16	(10.8)	3	(4.3)	12	(15.4)	15	(10.1)
Same	41	(66.1)	57	(67.9)	98	(66.2)	42	(60.0)	47	(60.3)	89	(60.1)
Decreased	17	(27.4)	15	(17.9)	32	(21.6)	25	(35.7)	19	(24.4)	44	(29.7)
Total responses	62		84		146		70		78		148	
n	103		111		214		103		111		214	

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

TABLE 13 *Number of times a week performing home exercise*

No. of times a week	6 months						12 months					
	Home	(%)	Class	(%)	Total	(%)	Home	(%)	Class	(%)	Total	(%)
0	23	(29.9)	24	(25.0)	47	(27.2)	32	(41.6)	29	(32.2)	61	(36.5)
1	4	(5.2)	9	(9.4)	13	(7.5)	9	(11.7)	11	(12.2)	20	(12.0)
2	12	(15.6)	17	(17.7)	29	(16.8)	8	(10.4)	15	(16.7)	23	(13.8)
3	6	(7.8)	14	(14.6)	20	(11.6)	10	(13.0)	11	(12.2)	21	(12.6)
4	7	(9.1)	3	(3.1)	10	(5.8)	4	(5.2)	5	(5.6)	9	(5.4)
5	7	(9.1)	6	(6.3)	13	(7.5)	4	(5.2)	3	(3.3)	7	(4.2)
6	4	(5.2)	2	(2.1)	6	(3.5)	1	(1.3)	2	(2.2)	3	(1.8)
7	12	(15.6)	19	(19.8)	31	(17.9)	9	(11.7)	14	(15.6)	23	(13.8)
14	2	(2.6)	2	(2.1)	4	(2.3)		(0.0)		(0.0)		(0.0)
Total response	77		96		173		77		90		167	
n	103		111		214		103		111		214	

TABLE 14 *Time spent performing home exercise*

Time (minutes)	6 months						12 months					
	Home	(%)	Class	(%)	Total	(%)	Home	(%)	Class	(%)	Total	(%)
<5	7	(12.1)	5	(6.1)	12	(8.6)	1	(2.1)	8	(11.3)	9	(7.6)
<10	17	(29.3)	33	(40.2)	50	(35.7)	19	(39.6)	23	(32.4)	42	(35.3)
<15	13	(22.4)	21	(25.6)	34	(24.3)	14	(29.2)	25	(35.2)	39	(32.8)
<30	17	(29.3)	19	(23.2)	36	(25.7)	11	(22.9)	12	(16.9)	23	(19.3)
≥ 30	4	(6.9)	4	(4.9)	8	(5.7)	3	(6.3)	3	(4.2)	6	(5.0)
Total	58		82	Total	140		48		71		119	

class group was unchanged, while for the home group it had reduced to once per week. At both 6 and 12 months there was no significant difference in the frequency of exercise (Mann–Whitney *U*-test $p = 0.96$ and 0.29, respectively).

The time spent performing the home exercise programme is given in *Table 14*. There was no evidence to suggest that the time spent exercising differed between groups. At both 6 and 12 months the median time spent exercising was between less than 15 minutes for both groups (Mann–Whitney *U*-test $p = 0.60$ and 0.34, respectively).

Ancillary analysis

Effect of self-instigated referrals

To assess the generalisability of the study, the self-instigated group was compared with the standard referral group (*Table 15*). There was evidence that patients in the self-instigated referral group were older but had better locomotor function with lower ALF scores. In addition, the self-instigated referral group had less walking pain at baseline. A subgroup analysis was carried out to investigate whether there was any difference in the effect of treatment for self-instigated referrals compared with standard referrals. This is important as it could be that the self-instigated referrals would be more motivated towards the class programme and hence showed a greater treatment effect. Alternatively, their less severe baseline symptoms might lead to a reduced treatment effect as less improvement was likely or necessary. *Table 16* summarises the treatment–subgroup interaction for the type of referral for the primary outcome and the main secondary outcome measures. The components of SF-36 listed are those in which an overall treatment effect was found.

The treatment–subgroup interaction term represents the difference between the treatment effect (class group mean – home group mean) for the self-instigated referrals compared with standard referrals. For ALF and its components VAS and WOMAC, a negative effect represents benefit of treatment. There was no difference between the groups for the outcomes. This means that the self-instigated referral subgroup appears to have a slightly reduced treatment effect compared with the standard referral. It should

TABLE 15 *Comparison of characteristics of standard and self-instigated referrals*

	Standard referral					Self-instigated					
	Freq.		**(%)**		***n***	**Freq.**		**(%)**			***p*** [a]
Women	82		(61)		135	43		(54)		79	0.37
	Mean	**SD**	**Min.**	**Max.**	***n***	**Mean**	**SD**	**Min.**	**Max.**	***n***	***p*** [b]
Age (years)	63.4	10.0	40.2	86.6	135	66.8	9.1	46.2	86.8	79	0.014
BMI	29.6	5.5	17.2	47.7	135	30.1	5.0	18.6	46.1	79	0.17
ALF	26.7	13.6	12.8	103.0	134	23.4	7.6	13.8	51.3	79	0.052
Flexion	116.7	15.2	70.0	145.0	135	115.80	14.90	45.00	140.0	79	0.69
VAS pain	65.3	18.8	17	100	135	58.5	15.7	10	97	78	0.007
WOMAC total	45.9	18.7	6	96	116	42.1	18.0	12	85	75	0.16
Pain	10.2	3.7	1	20	126	9.1	3.5	2	17	77	0.046
Stiffness	4.3	1.8	0	8	127	4.4	1.7	1	8	78	0.91
Physical function	31.2	14.1	2	68	118	28.6	13.8	4	63	75	0.19

[a] Chi-squared test.
[b] *t*-test.

TABLE 16 *Subgroup analysis of self-instigated referrals compared with standard referrals*

	Treatment subgroup interaction[a]	**95% CI**	***p***
ALF	1.38	(–0.83 to 3.59)	0.22
Flexion	0.48	(–2.63 to 3.59)	0.76
VAS pain	2.59	(–4.12 to 9.30)	0.45
WOMAC total	1.84	(–4.06 to 7.73)	0.54
Pain	–0.57	(–1.58 to 0.43)	0.90
Stiffness	0.69	(–0.02 to 1.40)	0.058
Physical function	1.43	(–3.06 to 5.92)	0.53
SF-36 PF	–2.43	(–10.47 to 5.61)	0.55
SF-36 P	–3.23	(–11.35 to 4.89)	0.44

[a] Difference between the treatment effect (class – home) for the self-instigated referral group compared with the standard referral group.

nevertheless be emphasised that this is only statistically significant for ALF sit-to-stand ($p = 0.047$). This finding may relate to the better prognosis of the self-instigated referral group.

Therapist and class effects

Only one physiotherapist was responsible for the interventions in this trial. Arguably, this will reduce the generalisability of the study. It should be noted that the therapist worked according to a well-defined protocol that was considered to represent typical clinical practice. However, given that the interventions were delivered to groups of patients rather than individually there may be some class effect, with patients in the same class tending to have more similar outcome. Referred to as intraclass correlation in statistical terminology, this can affect the precision of the estimates. Classes were small, varying in size from seven to 16 with a mean size of ten, so that any effect on precision is likely to be slight unless the ICC was great for that outcome.

A possible class effect was investigated using a three-level multilevel model[148] applied across all three follow-up time-points. This incorporated a level 3 variance term for the variation between classes and a level 2 variance term for the variation between patients. Preliminary results suggest that the ICC due to class was small (<0.02), leading to only a slight reduction in the precision of the treatment effect estimate.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Adverse events

Despite the wide range of abilities of the patients in the sample only one adverse event was recorded. One patient, while performing one of the home exercises, developed an inguinal hernia that required surgical repair. Following an interview with the patient it became apparent that the exercise had been performed incorrectly and did not represent any of the exercises that had been prescribed in the home exercise programme. This event led to a thorough search of the literature for previous reports of such an occurrence, with none being found. It was the opinion of the trial steering committee that the exercises, when performed as prescribed, presented minimal risk of producing inguinal herniation. The patient, the patient's GP and the local ethics committee were informed of the trial steering committee's findings.

Chapter 4

Cost-effectiveness analysis

Introduction

This chapter describes the cost-effectiveness analysis that was undertaken alongside the RCT. The objective of the analysis was to assess the cost-effectiveness of a class-based exercise programme supplementing the home-based programme when compared with just a home-based programme. Costs were estimated from the perspective of the NHS and effects were assessed in terms of health gain expressed as QALYs. A further aim was to estimate the probability that the class programme is cost-effective over a range of values of decision-makers' WTP for an additional QALY.

Methods

The economic analysis is based on the trial assessing the impact of a home-based exercise programme compared with a class-based programme. The patient sample, and therefore the effectiveness data, is the same as for the clinical trial that was detailed earlier. The analysis takes an NHS perspective with effects assessed in terms of health gains, measured in terms of QALYs. All costs fell within a 1-year period and therefore discounting was not appropriate. The trial was randomised with the patient as the unit of randomisation and also the unit of analysis.

Sources of data

Resource use

Data on resource use for the economic analysis were obtained from examination of patients' medical records and patient questionnaires administered at baseline, 1 month, 6 months and 12 months. Data from questionnaires were collected at attendance at outpatient appointments.

The cost of the intervention being evaluated in the trial was estimated from resource use data from the clinical trial applied to national payscale figures used in the Netten and Curtis document.[149] Resource use associated with giving the class-based intervention was estimated using average class size and duration. Both groups received input from senior 1 physiotherapists; for the economic analysis the additional cost of providing the class-based programme is the relevant cost. These costs include the capital and overhead costs associated with the additional physiotherapist time. In addition, any one-off expenses incurred by the patients were included in the analysis, and travel costs are examined in the sensitivity analysis.

Unit costs

Unit cost data were obtained from a number of sources. Inpatient cost per day and outpatient cost per visit for attendances were both based on national estimates.[150] Estimates were inflated to a 1999/2000 price base using the Health Service Cost index.

The cost of a GP visit was derived from estimates by Netten and Curtis.[149] The unit cost estimate includes cost of training as well as direct care support staff and is inflated to a 1999/2000 price base.

Health states and their value

The EuroQol 5 Dimensions (EQ-5D) instrument was used to measures patients' health states and to ascribe values to those states.[151] The EQ-5D questionnaire was given to patients (face to face) at baseline, and 1-, 6- and 12-month follow-up. The EQ-5D was also sent to patients at 3 and 9 months as a postal questionnaire. This instrument measures patient health status across five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Three possible responses (no problems, moderate problems or severe problems) are given by the patient for each of these dimensions, reflecting the patient's perception of their health state.

EQ-5D scores at baseline and follow-up were converted to a utility score based on a tariff derived from interviews with 3395 members of the UK public.[152] The two trial groups were compared in terms of mean changes (compared with baseline) in QALYs over the 12-month period. This was achieved by plotting the EQ-5D utility at baseline and at each intermediate point, and calculating the area under the curve to estimate QALYs gained (or lost) for each patient. Data from postal questionnaires (i.e. at 3 and 9 months'

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

follow-up) were not used as response rates were under 50% and the biases introduced from using these data could result in misleading conclusions.

Methods of analysis

Missing data and imputation

There is no formal test to verify the assumption that data are missing at random (MAR), and this assumption is often chosen as a starting point when data are missing.[153] If there is concern that data are not MAR, it is possible in principle to run the multiple imputation procedure using a model that reflects hypothesised differences between individuals with complete data and individuals with incomplete observations. The results obtained from the two models under the MAR and non-MAR assumption can then be compared to obtain a measure of the sensitivity of the inference to the missing data process. In practice, modelling a non-MAR process is not a trivial task, and it has been demonstrated that exploring the assumption of MAR relies on strong assumptions which are not themselves testable.[154] Therefore, for this analysis it was assumed that data were MAR.

Missing data were imputed using SOLAS (Statistical Solutions) using the propensity score method (a non-parametric approach). Multiple imputation replaces each missing value with several imputed values instead of just one. This gives a fuller reflection of the uncertainty surrounding which value to impute. For this analysis five datasets were generated, each with a different set of imputed values. Values were imputed for each of the dimensions of the EQ-5D (rather than total score) and for each missing item of resource use (rather than total cost).

Incremental cost-effectiveness ratios and net monetary benefits

Traditionally, cost-effectiveness analysis has involved the calculation of incremental cost-effectiveness ratios (ICERs), where mean differences in costs and effects under the treatment and control arms were presented with 95% confidence intervals. The ICER is calculated from the mean difference in cost and effect between the two treatment options. Algebraically, the ICER is represented as:

$$\text{ICER} = \frac{C_1 - C_0}{E_1 - E_0} = \Delta C / \Delta E$$

where C_1 are sample mean costs and E_1 are sample mean effects. These statistics are calculated in this analysis. However, interpretation of ICER statistics that cover more than one quadrant of the cost-effectiveness plane is troublesome, and recent papers have advocated the net benefit approach to cost-effectiveness analysis.[155,156] This approach can be performed for this study quite simply. From the five data sets generated through multiple imputation, the net monetary benefit (NMB) was calculated for each group. For specific levels of a decision-maker's maximum willingness to pay for a QALY, the NMB of a strategy can be estimated using the equation:

$$\text{NMB} = (\lambda * \text{QALYs}) - \text{Cost}$$

For instance, if treatment A has a mean cost of £100,000 and generates a mean of 5 QALYs with a QALY valued at £30,000, then the NMB associated with treatment A is (5 × £30,000) – £100,000 = £50,000.

It is also possible to express NMB at the patient level by multiplying each patient's QALY score by the decision-maker's assumed maximum value and subtracting that patient's costs. The patient-level NMB is used in the derivation of the cost-effectiveness acceptability curves (CEACs), described below.

Clearly, the NMB is dependent on the value that is placed on the QALY, but results of the analyses indicate how sensitive the results are to changes in this value. However, the uncertainty surrounding the NMB statistic can be used to identify the probability that a strategy is cost-effective using the CEAC.[157] The CEAC is a graphical representation of the probability of an intervention being cost-effective over a range of monetary values for a decision-maker's WTP for an additional unit of health gain. The probability of an intervention being cost-effective will differ according to the valuation that the decision-maker places on a QALY. For this analysis, the values zero, £1000, £10,000, £20,000, £30,000, £50,000 and £100,000 were used as a range of the decision-maker's WTP for a health gain of 1 QALY. The value zero is equivalent to a comparison of the groups in terms of total costs, as outcomes are effectively not considered (valued at zero).

Results

Resource use

Mean levels of resource use are presented in *Table 17*. These estimates utilise resource use data estimated using the multiple imputation method

TABLE 17 *Mean resource use in the two groups over the 12-month study period*

	Home-based group (*n* = 103)	Class-based group (*n* = 111)
GP home visits	0.30	0.09
GP surgery visits	6.94	6.09
District nurse visits	0.06	0.00
Practice nurse visits	1.86	1.27
Day hospital attendances	0.26	0.13
Day-case attendances	0.08	0.23
Inpatient length of stay	0.46	0.21
Outpatient attendances	0.75	1.11
A&E attendances	0.14	0.17

and are the means across five data sets. For the majority of these resource use variables, the class-based programme resulted in a reduction in resource use, which ultimately results in a difference in total cost between the two groups.

Unit costs

Unit cost estimates used in the analysis are shown in *Table 18*. The sources for these estimates are detailed earlier in this chapter (section 'Unit costs', p. 31).

TABLE 18 *Unit costs of resources used*

	Unit cost (£)
GP home visits (cost per visit)	59
GP surgery visits	19
District nurse visits	20
Practice nurse visits	10
Day hospital attendances	74
Day-case attendances	355
Inpatient cost per day	Various (mean 348)
Outpatient attendances	Various (mean 77)
A&E attendances	61

Health states

The health states of the patients are shown in *Table 19*. The class-based intervention appears to have a large impact on anxiety and depression; while the intervention group showed a marked increase in the percentage in the highest category, the percentage in the control group fell considerably. Conversely, patients in the control group performed better in terms of mobility and self-care than did those in the class-based intervention group, although paradoxically the control group experienced a fall in the percentage who had no problems with usual activities, while the intervention group had an increase in this percentage. A possible explanation is that anxiety and depression have a larger influence on usual activities than do mobility and self-care; this is only a hypothesis and more research would be required to confirm the relationship between the dimensions.

Based on the estimates shown in *Table 20*, changes in QALYs can be estimated as in the following section.

TABLE 19 *Percentage of patients in each EQ-5D dimension by group at baseline and 12-month follow-up*

	Class-based (*n* = 111)						Home-based (*n* = 103)					
	% of patients in baseline health state			% of patients in follow-up health state			% of patients in baseline health state			% of patients in follow-up health state		
	1	2	3	1	2	3	1	2	3	1	2	3
Mobility	17.8	81.8	0.4	20.2	79.8	0.0	13.2	86.8	0.0	18.8	81.2	0.0
Self-care	69.2	29.5	1.3	61.4	38.6	0.0	61.0	38.8	0.2	70.3	29.7	0.0
Usual activities	20.0	73.0	7.0	23.6	74.4	2.0	19.4	76.5	4.1	13.6	81.6	4.9
Pain/discomfort	2.2	72.0	25.8	2.7	87.7	9.5	0.0	69.5	30.5	3.1	76.3	20.6
Anxiety/depression	48.6	46.2	5.2	63.2	32.1	4.7	54.0	38.0	8.0	44.9	51.5	3.7

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

TABLE 20 *Mean EQ-5D score at baseline and follow-up by group*

	Baseline	1 month	6 months	12 months
Home-based programme	0.50	0.52	0.54	0.53
Class-based programme	0.54	0.60	0.58	0.58

Quality-adjusted life-years

As with the resource use data, mean change in the number of QALYs is presented in *Table 21*. Both groups are slightly better off in that they report an increase in QALYs over the 12-month period. These estimates are based on merged values from the five data sets.

These differences are very small and do not approach conventional levels of statistical significance, with a standard error around the difference in the mean QALY gain per patient of 0.0189. It is feasible that the use of the EQ-5D and QALYs is not sensitive enough in this patient population to pick up differences in patients' health-related quality of life. However, these results indicate that the class-based group performed slightly better in that the gain in QALYs was greater in this group than in the home-based group.

Total cost

The difference in total cost between the two groups is presented in *Table 22*. These estimates are again based on the merged data set and include the cost of the intervention. There is again, considerable uncertainty around these estimates. The standard error around the difference in the total mean cost per patient is £100.32.

TABLE 21 *Mean change in QALYs per patient over the 12-month period*

	Mean QALY gain
Home-based programme	0.022
Class-based programme	0.045

TABLE 22 *Total costs per patient in the two groups over the 12-month period*

	Class-based programme (n = 111)	Home-based programme (n = 103)
Total cost	£440.04	£445.52

ICER

In this instance, the class group is associated with a slightly better QALY profile and a slightly lower cost. Specifically, the class group has a 0.023 QALY gain compared with the home-based group, and a reduced cost of around £5 per patient. In this instance, calculation of the ICER is inappropriate.

However, there is a large degree of uncertainty around these results and neither the improved patient outcomes nor the reduction in costs would approach traditional levels of statistical significance. Therefore, to deal adequately with uncertainty the NMB approach was used and CEACs were generated. The results of these analyses are presented below.

NMBs and CEAC

Clearly, the value of NMB is dependent on the value of a decision-maker's WTP (λ) for an additional QALY. The probability of an intervention being cost-effective will also depend on this value. The CEAC is presented in *Figure 6*. λ is varied between zero (where gains in QALYs are not valued at all) and £100,000. In the base-case analysis, represented by the lower of the two lines, it can be seen that a zero value of λ gives a probability of the class-based programme being cost-effective of just over 50%. In effect, this means that there is a probability of only just over 50% that the class group was cost-saving, as no value was placed on QALY gains. However, the probability of the class being cost-effective increases as the value placed on λ increases (as the class is associated with an improved QALY profile). At λ = £30,000, an estimate frequently stated to be the borderline value for the NHS, the class-based programme has a probability of over 70% of being cost-effective. Indeed, for all plausible values of λ, in the base-case analysis, the class group is more likely to be cost-effective than the home-based group.

Sensitivity analysis

Although the form of stochastic analysis performed above addresses a large amount of uncertainty in the analysis, it is still appropriate to perform sensitivity to allow for variability and methodological uncertainty.

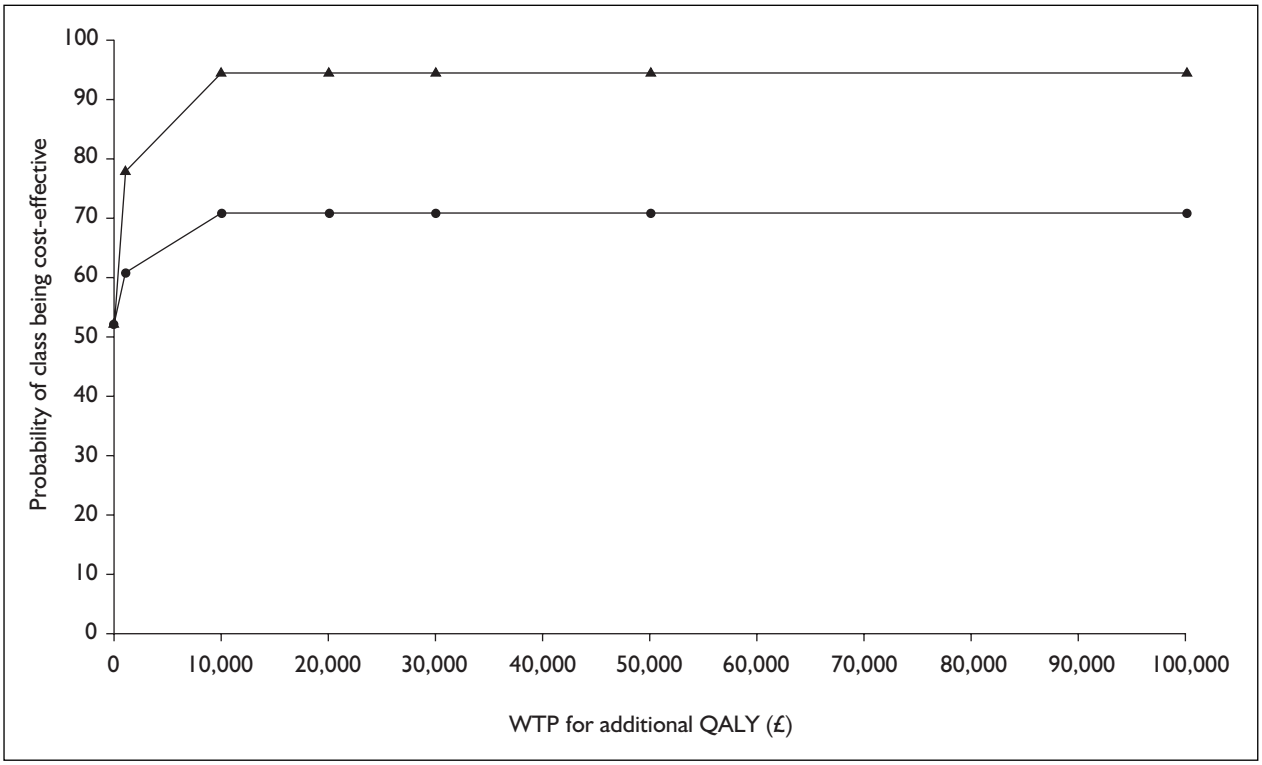

FIGURE 6 *CEAC for the two interventions. —●—, probability of class programme being cost-effective for given levels of WTP; —▲—, complete case analysis.*

Complete case analysis

This analysis is based on the sample of patients with complete cost and outcome data ($n = 74$), with 30 patients in the home-based group and 44 in the intervention group. At least some cost data were missing for 90 individuals, with at least some outcome data missing for 83 individuals. While this appears to be a large amount of missing data, the majority of cost data that were missing were the answers to one question, rather than whole questionnaires; similarly, with the outcome data, the missing data were frequently only one EQ-5D dimension at either baseline or follow-up. The point estimates in this instance show similar results to the imputed data. The results of this analysis were transformed into an NMB framework and are shown in *Figure 6*. These results show the class-based group to have a higher probability of being cost-effective than the analysis using imputed data, but would not alter the decision at any value of λ. The reduction in cost in this analysis was only marginally in favour of the intervention, while this analysis also demonstrated a more favourable QALY change of 0.12 compared with the control group. This result is reinforced by the analysis of the VAS results, which showed the class-based programme improving by 0.77 points compared with the home-based programme.

Inclusion of travel costs

Travel costs were not included in the base-case analysis. The rationale for this exclusion is that if the intervention were to be rolled out across the NHS, these travel costs (invariably incurred in and around the Manchester area) would not be generalisable to other settings. However, it is feasible that these travel costs would have an impact on the probability of the intervention being cost-effective. A £50 travel cost was therefore imposed on each individual in the intervention group. The results of the sensitivity analysis appear on the lower line of the CEAC, and show that where a decision-maker's WTP for a QALY is very low, the probability of the intervention being cost-effective is reduced. However, at a WTP of £20,000-30,000 per QALY, the inclusion of travel costs has little impact, with the probability of the intervention being cost-effective being over 65%.

Conclusion

There is little evidence in the published literature of the cost-effectiveness of patient exercise

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

programmes in the treatment of osteoarthritis. Lord[158] conducted a full economic evaluation of a primary care-based education programme for patients with osteoarthritis. The authors found no significant differences in patient outcomes, but a significant increase in costs associated with the education programme, and concluded that this supported the hypothesis that GP-based patient education programmes are not cost-effective. However, the authors used a cost-minimisation analysis as there were no significant differences between groups in the WOMAC score. This type of analysis has been criticised[159] as inappropriate where the trial was not designed to show equivalence. In addition, utility values were not assessed for the groups.

The above analysis shows that, for most reasonable values of a decision-maker's WTP for an additional QALY, the class-based programme is likely to be cost-effective. This is due to both a small reduction in the costs and a slight improvement in the QALY score in the class-based group compared with the home-based group. This is achieved by a reduction in primary care contacts in the class-based group and little difference in hospital-based attendances. However, there is considerable uncertainty around this estimate and a probability of approximately 30–35% that the intervention is not cost-effective.

Chapter 5
Discussion

Primary clinical outcome: ALF score

The supplementation of a home exercise programme with a class-based exercise programme resulted in a reduction in the time taken to complete the locomotor functions of the ALF outcome. This represents an improvement in locomotor function. At post-treatment, 6 months and 12 months the estimated effect of treatment was a reduction of 3.45 (95% CI 2.44 to 4.46), 2.56 (1.31 to 3.81) and 3.68 (2.50 to 4.87), respectively, after adjustment for baseline ALF, BMI, age, gender and source of referral. Comparing the adjusted class treatment with the home group suggests that the reduction in ALF scores was 14%, 11% and 15% for post-treatment, 6 months and 12 months, respectively. This magnitude of treatment effect is of a size on the threshold of a level considered to be a minimum clinically important difference.[160] Thus, the supplemented group experienced a small but greater improvement that was maintained over the 12-month review period, suggesting both short- and long-term benefit.

Comparison with previous work is impossible, as no similar trial has been undertaken. The trial with the closest design to the present study involved the comparison of individual physiotherapy sessions with a group-based class exercise programme.[161] However, that trial's primary aim was to compare a no-treatment control with intervention (individual physiotherapy sessions and class-based exercise) and so was considerably underpowered to detect a difference between the two intervention groups. No statistically significant difference between groups was detected. The Fitness Arthritis and Seniors Trial (FAST)[57] compared two exercise interventions (aerobic and resistance exercise groups) with a health education programme and found a moderate-sized difference between the groups for observed walking speed, although comparing these effects with this study is difficult owing to differences in the intensity, duration and frequency of the trial's intervention.

The majority of reported trials have used a no-treatment control group and thus between-group differences would be expected to be greater than in this study, where both groups received therapeutic intervention. However, despite this methodological difference small to moderate between-group differences were demonstrated in the present study. This may suggest that the class-based exercise programme was at least as effective as and possibly more effective than some of the programmes investigated previously.[3,58,139]

Secondary clinical outcomes

Walking pain

Supplementing a home exercise programme with a class-based exercise programme led to greater reduction in the pain experienced while walking. At post-treatment, 6 months and 12 months the estimated effect of treatment was a reduction of 18.1 mm (95% CI 14.4 to 21.8 mm), 11.4 mm (7.1 to 15.6 mm) and 15.2 mm (11.7 to 18.1 mm), respectively. Comparing the adjusted class treatment with the home group suggests that the reduction in VAS scores was 33%, 21% and 25% for post-treatment, 6 months and 12 months. Thus, although the benefits of supplementation declined over the 12-month review period long-term benefit remained. The magnitude of treatment effect was greater than recommended minimum clinically important difference.[160] Again, a difficulty in comparing between-group differences with previous studies exists as no trial has previously compared similar interventions. The two studies that were most comparable to the present study[57,161] both described small differences in pain score improvement between two exercise treatments; however, methodological differences make meaningful comparisons difficult.

Self-reported disability and health (WOMAC, SF-36 and EuroQol)

The supplemented group demonstrated statistically significant greater improvements in total WOMAC score (pooled estimate –4.84, 95% CI –1.97 to –4.84) and for each dimension immediately post-treatment (pain –1.18, –0.52 to –1.85; stiffness –0.46, –0.12 to –0.81; physical function –3.39, –1.20 to –5.58). Treatment effects were evident for total WOMAC score and each dimension immediately post-treatment and at 12-month review, apart from the stiffness

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

dimension, which showed no effect at 12 months. These results represent a smaller change in the WOMAC dimensions and total score than in other studies. Previous authors have reported moderate to large improvements in pain and physical function dimensions, although comparisons were made with a non-intervention group[161–164] and therefore smaller differences in the present study might reasonably have been expected. Certainly, at post-treatment assessment the between-group differences for the individual dimensions and total score ranged between 11 and 16%, and if one accepts the recommendation that changes of approximately 20% are required to suggest a "clinically important" difference,[111] the statistically significant between-group differences identified with this outcome can be accepted as being of small clinical effect.

Only two of the SF-36 dimensions demonstrated a statistically significant treatment effect. The pain and physical function dimensions demonstrated small but statistically significant pooled treatment effects of 7.39 (95% CI 3.43 to 11.34) and 5.61 (95% CI 1.69 to 9.52), respectively. These treatment effects are of the same magnitude as those demonstrated by the pain and physical function dimensions of the WOMAC. A treatment effect was identified for the energy and vitality dimension at 6 months, suggesting that the supplemented group had marginally greater energy and vitality at this review. It is likely that this finding is spurious as no obvious explanation for this transient treatment effect is apparent. There was no significant change in health status as measured by the EuroQol health VAS, with neither group showing any change in health status. This lack of change may represent a lack of sensitivity of the instrument in this patient group; however, this finding is similar to the trend observed with the SF-36 instrument.

Strength, balance and range of movement

Improving muscle strength is one of the primary aims of exercise treatment and one of the primary recommendations for treatment of patients with knee osteoarthritis.[26,46,54,56] A convincing body of evidence exists that suggests exercise treatment, incorporating a degree of muscle strengthening, produces a small to moderate improvement in pain and function in knee osteoarthritis.[25,26,60] Although the effectiveness of exercise as a treatment modality in knee osteoarthritis is generally accepted, the mechanism by which improvements in pain and function are produced is far from established. However, a common theme of the literature is that muscle strengthening produces an improvement in the sensorimotor control of the knee joint during functional activities, leading to a reduction in shock impact on the joint, which in turn reduces the pain elicited during these activities.[121,165–168]

Treatment effects were observed for balance, strength and range of movement immediately post-treatment, suggesting that the supplemented group had small but statistically significant greater improvement. None of the outcomes demonstrated statistically significant differences at the 6- or 12-month review, suggesting that supplementation led to only temporary differential benefit for these outcomes. The pooled estimates for balance (AP GMean ratio 0.90, 95% CI 0.81 to 0.99, ML GMean ratio –0.26, –0.15 to –0.38) and range of movement (mean difference 2.7, 95% CI 1.2 to 4.4) suggested that there may be a lingering differential improvement for these outcomes, but of a small scale. The pooled estimate for strength showed no significant difference in GMean ratio (1.06, 95% CI 0.94 to 1.19), suggesting that the difference observed post-treatment was not maintained at the 6- or 12-month review.

In this study patients demonstrated a short-term improvement in muscle strength. At post-treatment assessment there was a statistically significant difference between the two treatment groups, with the class group demonstrating greater strength. The size of this difference was small to moderate (GMean ratio 1.06, 95% CI 0.94 to 1.19), but at the 6- and 12-month assessments was reduced to a small and non-significant difference ($p > 0.05$). This finding suggests that supplementation led to a short-term differential improvement in lower limb strength, but when the intense exercise of the class-based programme was no longer performed this differential benefit was quickly lost. It is well established that intensity of exercise has significant bearing on the degree of strengthening achieved;[169] consequently, equivocal, long-term gains in muscle strength might be expected from two groups of patients performing equivocal home exercise programmes.

Patients with knee osteoarthritis have reduced knee flexion compared with age-matched controls[45,61] or their own asymptomatic knee,[45,127] with reduced knee flexion being shown to have a weak association with observed and self-reported disability.[127] Patients with knee osteoarthritis demonstrate considerably less knee flexion when

performing locomotor functions and instead develop compensatory mechanisms to achieve functional ability.[61] The patients in this study demonstrated very similar amounts of knee flexion (116 degrees, SD 15 degrees) to values reported by Messier and colleagues[45] (118 degrees, SD 17 degrees), who used the same methodology to obtain data. However, two other studies using different methods of measuring range demonstrated greater[127] and lesser degrees of flexion.[61] Differences in subject age, BMI and methodologies of the studies may explain these differences.

The supplemented group demonstrated a small but statistically significant greater improvement in range of knee flexion immediately post-treatment (3.7 degrees, 95% CI 2.0 to 5.5 degrees). No difference in treatment effect was observed at the 6- and 12-month reviews. These findings compare very well with the findings of the five previous exercise trials that have included range of movement as an outcome assessment. Unfortunately, all of these trials were underpowered to detect even a large difference in knee flexion, with all[58,59,170,171] but one[172] finding no significant difference in knee flexion. The one exercise trial that demonstrated a difference between a home exercise programme and a control group[172] involved the patients taking a regular course of NSAIDs in addition to exercise. However, despite this analgesic influence, the degree of between-group difference was of a similar magnitude to that in the present study, with an initial improvement of five degrees being reported.

It would appear that this study has concurred with previous work in presenting evidence to suggest that knee flexion range of movement was only improved by a small degree with exercise programmes aimed at strengthening lower limb muscles. Although a small number of exercise trials included an element of joint stretching within their interventions, none of them used range of movement as a primary outcome measure. This lack of emphasis, which was also a feature of this study, means that the effectiveness of a deliberately designed stretching programme on increasing knee flexion and improving disability has not been established. This presents another area for further investigation as the available literature has not examined stretching as an effective treatment option and consequently its effectiveness in the treatment of knee osteoarthritis remains unquantified.

Compliance with home exercise

The compliance of patients with exercise programmes is "important in degenerative conditions since long-term efficacy of treatment depends partly on compliance with the therapeutic exercises recommended for the patients".[134] Unfortunately, in an outpatient setting, non-compliance with exercise therapy is particularly high,[173] with long-term compliance being even more difficult to achieve as patients no longer receive motivation from their therapists and do not receive feedback about their progress.[173] Non-compliance has been defined as "a failure by patients to follow advice"[133] and non-compliance with physiotherapy regimens in the treatment of knee osteoarthritis is well documented.[133,134]

As part of the assessment of compliance, attendance rates for the class group were recorded. Median attendance rate was 81% (interquatile range 62 to 94%), which compared well with previous work.[50,56,57] At both 6 and 12 months there was no significant difference in the frequency of home exercise performance between the groups (Mann–Whitney U-test $p = 0.96$ and 0.29, respectively). There was also no evidence to suggest that the time spent exercising did not differ between groups. At both 6 and 12 months the median time spent exercising was less than 15 minutes for both groups (Mann–Whitney U-test $p = 0.60$ and 0.34, respectively). There was, however, some suggestion of increased physical activity levels in the class group. Although similar proportions reported no change in each treatment group, a greater proportion reported increased physical activity levels in the class group. When an ordinal logistic model[147] was fitted the common odds ratio was 1.82 (95% CI 0.92 to 3.62, $p = 0.09$) at 6 months and 2.07 (95% CI 1.07 to 4.00, $p = 0.03$) at 12 months, suggesting that the class group was indeed describing greater physical activity levels at both reviews.

Of the patients who continued to undertake the home exercise programme, less than 10 minutes was spent undertaking the home exercises, twice a week, in the majority of patients of each group. These figures are quite a departure from the recommended daily exercise programme that should realistically have taken approximately 15 minutes to perform; thus, compliance with the home exercise programme could be classified as poor, a finding that has been reported by several authors.[133]

Summary of economic evaluation

The group with the supplementary class-based exercise programme was associated with a slightly

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

better QALY profile and a slightly lower cost compared with the home-based programme alone. The class supplementary programme was very slightly less expensive, as there was a reduction in primary care contacts with little difference in hospital-based attendance costs compared with the home-based group. Thus, the supplementary class-based programme was considered a dominant case in that it was less expensive and improved patient outcomes. In addition, for most reasonable values of a decision-maker's WTP for an additional QALY, the class-based programme was likely to be cost-effective. However, there is considerable uncertainty around this estimate and a probability of approximately 30–35% that the intervention is not cost-effective.

Explanations of findings

Why did the supplementation of the home exercise programme with a class-based exercise programme lead to greater improvement in locomotor function? If one considers the multifactorial nature of the physical and psychosocial components of knee osteoarthritis, it becomes apparent that determining the relative contribution of these elements to the observed improvement is impossible. However, although the treatment interventions were likely to have influenced psychosocial factors, they were primarily physical interventions and consequently physical factors might have been expected to have the greatest influence on the improvements in pain and function observed.

Physical factors

Deficit in the neuromuscular control of the knee has been shown to be evident in patients with knee osteoarthritis,[121] and is seen as an important factor in the production of pain[174] and in the reduction in locomotor function.[167,175] Efficient neuromuscular control requires efficient coordination of strong muscles,[176] and interventions that have increased muscle strength and improved sensorimotor control have been shown to improve pain and reduce locomotor dysfunction.[56,177] The patients in the present study demonstrated improvements in muscle strength and balance ability after treatment with greater benefits being demonstrated post-treatment by the class group. The class group demonstrated a correspondingly greater improvement in locomotor function and a greater reduction in pain at post-treatment assessment.

Improvement in muscle strength has been shown to improve locomotor functional ability.[37,167] This is due to a greater ability to generate the muscular forces required to move body weight, and leads to an increase in the speed and efficiency with which functional tasks are performed1.[76,178] Patients may demonstrate a greater ability to generate muscular force owing to a reduction in the arthrogenic inhibition that accompanies knee osteoarthritis.[179] Hurley and Scott[37] demonstrated that a rehabilitation programme, not dissimilar to the class group in the present study, reduced the degree to which the quadriceps muscle was inhibited, and although this was not assessed in this trial it may have been a factor in the improved strength demonstrated in the present study. Strong musculature around the knee joint also provides functional stability for the joint during activity.[179] Functional joint stability is the stability of the joint during activities, and requires muscular contraction to protect the joint by reducing excessive shearing and straining movements with coordinated and powerful muscular contractions.[121] Increasing muscular strength will improve the functional stability of the joint and thus reduce damaging shearing and straining movements within the joint, leading to reductions in pain during activity.[121]

Strength gains are accelerated by increasing both the intensity of the exercise and the frequency with which it is conducted.[169] Consequently, it would seem reasonable to expect the class group to have gained greater strength during the treatment, as patients in this group undertook more exercise than the home group. Furthermore, the class programme exercise was more intensive than that undertaken by the home exercise group. The class group's decline in strength, to the levels of improvement demonstrated by the home group at the 6-month assessment, may have been due to the lack of continued frequent and high-intensity exercise, particularly as declines in strength have been demonstrated with reductions in the demand of exercise programmes.[180]

Balance had improved at post-treatment assessment for both groups. Again, the class group demonstrated greater improvement than the home group, suggesting that neuromuscular control was greater for these patients following treatment. Improvements in balance have been shown to reduce the variability of the forces and moments experienced by the knee during gait,[181] and thus can potentially reduce the pain experienced during walking and improve the speed and efficiency of this locomotor function.[56]

Neuromuscular control has been shown to be most effectively improved with the use of exercises that deliberately target the sensory systems involved in the maintenance of balance.[182] Both groups undertook exercises that were designed to challenge the sensorimotor control of balance; however, the frequency and intensity of the challenge to balance were greater in the class group. Both groups undertook exercises that aimed to improve static balance as part of their home exercise programme, but only the class group undertook exercises aimed at improving dynamic balance. Dynamic balance was challenged with the use of wobble boards and during accelerated walking exercises undertaken during the class programme. This may explain why improvement in neuromuscular control was greater in the class group at post-treatment assessment, but after 6-months, owing to the lack of continued stimulus of the class-based exercises, was not different from the home group.

Exercise treatment has been shown to improve aerobic work capacity, even with exercise programmes that were not aerobic in nature and instead used resistance exercises similar to the exercise programmes adopted in the present study.[55] Patients with knee osteoarthritis have been shown to have reduced aerobic work capacities to the extent that aerobic threshold may be reached in the course of daily activities.[46,55,183] Becoming breathless by simply walking up a few steps reduces the physical activity undertaken by patients with knee osteoarthritis, and although this parameter was not assessed in the current trial, it may have been influenced by the treatment. The class group undertook a shuttle-walking test 'warm up' at the beginning of the class. This testing procedure encouraged patients to accelerate their walking over a 5-minute period and has been used extensively as a method of testing and improving aerobic capacity.[143] It is likely that the class group received benefit from this part of the programme, with this benefit contributing to the superior improvements demonstrated at post-treatment assessment.

At post-treatment assessment the link between physical reasons for improvement and actual improvement in locomotor function and reduction in pain appeared to be strong. Improvement in locomotor function and reduction in walking pain were greater in the class group, and were accompanied by greater improvement in strength and neuromuscular control, suggesting that physical improvement had strongly contributed to the observed improvements. However, at the 6- and 12-month assessments, although there continued to be superior improvement in locomotor function and walking pain in the class group, all strength and neuromuscular control measures were not significantly different from the home group. This suggests that the influences on locomotor function and pain at 6 months were not solely physical and that other factors had led to the maintenance of this differential improvement; there are likely to be other factors influencing the effectiveness of the two treatments and these factors are likely to be psychosocial in origin.

Thus, it can seen from the previous discussion that as the treatment programmes were multidimensional and were aimed at improving the patients' strength, proprioception and balance, many possible physical explanations for the improvements demonstrated could be considered. It is likely that all of these mechanisms were influenced by treatment, to varying degrees, and although these mechanisms may explain some of the improvement demonstrated, other factors must be considered. In addition to the physical factors influencing treatment effectiveness, several psychosocial and environmental factors must be incorporated into this discussion.

Psychosocial factors

Certain personality traits have been shown to influence the degree to which knee osteoarthritis affects patients.[46] It has been shown that there is a relationship between anxiety, depression and pain severity, and that joint pain and disability in older people depend as much on factors such as depression and isolation as they do on the severity of joint damage.[5,12] In a later study the same authors again found that anxiety in conjunction with the patient's perception of their 'helplessness' was associated with the degree of disability experienced.[184] Rehabilitation programmes that have incorporated advice and education sessions as well as exercise have been shown to reduce anxiety and depression and increase self-efficacy in patients with knee osteoarthritis.[30,34,48,185] It is likely that the improvements demonstrated by each group in the present study were in part due to the benefits gained from the advice and education sessions received. However, each group received equal amounts of advice and education, and so the differential improvement between the groups is not fully explained by this factor alone.

Improvements in both compliance with exercise and locomotor function have been linked with the degree of social support received by the patient[48,185,186] both in terms of the support

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

received at home and during the treatment sessions. The class group received considerably greater support and social contact from the treating physiotherapist and from other patients, and so differential improvement between the groups may have been considerably influenced by this factor. In addition, issues of expectation of benefit have been shown to have a large influence on exercise compliance and subsequent improvement.[133] The trial had an open design, with patients in either group being aware of approximately what the other group was receiving. Consequently, the patients in the class group may have felt that the supplemented programme was more likely to be effective owing to the greater degree of attention that they were receiving, and consequently expected greater improvement from the treatment than did the home group.

Despite the likelihood that the class group benefited from greater 'positive' psychosocial influences during treatment, compliance with the home exercise programme at 6- and 12-month assessments was not different between the groups. This might suggest that by 6 months psychosocial influences on exercise behaviour were not significantly different between the groups and so an explanation of why a differential improvement between locomotor function and walking pain between the groups still existed is not simple. The explanation of this finding is likely to be multifactorial and involve influences from both physical and psychosocial areas. An analysis of the psychosocial influences in knee osteoarthritis was not designed to be a feature of the present study, but further investigation of these factors provides an exciting area for further research as the influence of psychosocial factors may be large.

Overall implications of the study

Validity

The main threats to the validity of the trial were controlled for by adopting a blinded assessment, RCT methodology. Potential threats to the trial's validity were included in the minimisation allocation process, and another factor (self-instigated referrals) that arose as a result of a change in referral patterns was included as a covariate in the between-group analysis, so that its influence might be assessed.

To assess the effect of the influence of the subgroup of patients who self-instigated their referral for treatment an ancillary subgroup analysis was carried out to investigate whether there was any difference in the effect of treatment for self-instigated referrals compared with standard referrals. This was considered important as it was possible that the self-instigated referrals would be more motivated towards exercise and hence showed a greater treatment effect. There was no difference between the groups for the outcomes apart from sit to stand, which showed a very small negative effect. This means that the self-instigated referral subgroup appeared to have a similar treatment effect compared with the standard referral group, suggesting that the subgroup of self-instigated referral patients had not unduly influenced the generalisability of the trial findings.

The outcome measures used were selected after reviewing the literature for their appropriateness, reliability and proven validity with this population. Outcome measures that had not been previously validated were assessed for reliability and validity before being used in or during the course of the trial. Practice or learning effects were identified before the start of the trial and familiarisation visits incorporated to reduce this threat. Testing effects were minimised and analysed by reducing the number of assessments that were required for the majority of the patients, stratifying equal numbers of full and core assessment patients into each treatment group, and by assessing the effect of the extra assessments during analysis. Outcome measures were analysed to establish their measurement error and the magnitude of their smallest detectable difference. The trial's primary outcome measure was shown to have a low smallest detectable difference (9.5%), smaller than the treatment effects observed in the trial.

The trial was an open design, with blinded assessment; thus, a degree of control for experimenter expectancy was ensured. However, without a non-intervention control group the chance of a systematic error due to an unconscious belief, on the part of the lead investigator, that both exercise programmes should improve symptoms, may have led to a falsely high improvement within both groups. This was combated by ensuring that a standardised assessment protocol was adopted for each assessment but an expectation of effect or willingness to please the investigator, the Avis effect,[187] may also have led patients to perform in a manner that was superior to their normal locomotor function. Random allocation to treatment group would have controlled for the influence on between-group effects, but this factor needs to be considered when interpreting any within-group analysis.

Despite the wide range of abilities of the patients in the sample, only one adverse event was recorded. One patient, while performing, incorrectly, one of the home exercises developed an inguinal hernia that required surgical repair. This event led to a thorough search of the literature for previous reports of such an occurrence, with none being found. It was the opinion of the project team that the exercises were unlikely to have caused the event and the patient, patient's GP and the local ethics committee were informed of this. Despite this one incident the intervention and assessments appeared appropriate, comfortable and enjoyable for the patients.

The trial had strong generalisability to the clinical situation. To control for threats to the trial's validity the selection criteria were designed to include typical patients with knee osteoarthritis who might be referred to physiotherapists for treatment. Selection criteria were designed following a review of the literature and in discussion with expert clinicians in the field. While non-stringent selection criteria allowed the creation of a heterogeneous sample, they excluded patients whose inclusion may have provided a threat to the internal validity of the trial. The two interventions were designed to be representative of current clinical practice after reviewing the literature and discussion with expert clinicians in the field. The programmes were considered to represent best current clinical practice and that a pragmatic trial evaluating differences between the provision of the two programmes would be most useful to clinicians in the field.

Although the validity of the trial may have been threatened by the individual nature of the exercise programme and the capabilities of the treating physiotherapist, it was considered impossible to include multicentre treatment as a method of reducing this threat, because of time and resource constraints. Arguably, the individual nature of the provision of the exercise programme may have reduced the generalisability of the study. It should be noted that the therapist worked according to a well-defined protocol that was considered to represent typical clinical practice. However, given that the interventions were delivered to groups of patients rather than individually there may be some class effect, with patients in the same class tending to have more similar outcome. Possible class effect was investigated in an ancillary analysis, using a three-level multilevel model[148] applied across all three follow-up time-points. The ICC due to class was small (<0.02), leading to only a slight reduction in the precision of the treatment effect estimate and suggesting that the influence of the individual therapist and particular class groups was minimal.

Analysis of clinical effectiveness was structured to adjust for loss to follow-up using the statistical model described. A more conservative statistical approach to this issue was also reported by calculating the ITT analysis values for the trial's primary outcome measure. By using the LVCF method of imputing missing data a smaller treatment effect was observed. Although this value represents a small treatment effect it is still greater than the 10% recommended as a minimal clinically important difference (MCID) and consequently does not threaten the conclusion that the supplementation of home exercise with a class-based exercise programme leads to small but clinically meaningful improvement in locomotor function.

Minimal clinically important differences

To address the difficult question of whether treatment effects were of a magnitude that might be considered clinically significant an investigation of this area's MCIDs was undertaken. An MCID has been defined as the smallest difference in an outcome measurement that is perceived as beneficial and, in the absence of excessive side-effects, would lead to a change in the patient's management.[188] The process requires that the difference observed is assigned an importance using a valid method of rating.[188] Nine methods for determining MCIDs have been described, with techniques ranging from patient perspective rating to clinician consensus rating, with each of the methods having operational advantages and disadvantages.[188]

In the field of knee osteoarthritis, expert clinician consensus, using the Delphi approach, has been undertaken for MCIDs with certain key outcome measures.[160] In 1992 this eminent consensus committee recommended that an MCID for overall pain assessment, using a VAS for pain, was 15 mm and that a difference in 8-m walk time should be at least 1.6 seconds (20%). Thus, the between-group difference at post-treatment assessment, for the VAS pain score, of 18 mm (33%) was above these MCIDs, while the primary outcome of ALF score was slightly under the recommended threshold at 3.5 seconds (14%). At 12-month review the ALF score was slightly under the threshold at 15% difference, while the VAS pain score remained above the clinically important threshold (15.2 mm). In the most recent studies of

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

the effectiveness of exercise in knee osteoarthritis sample sizes have been calculated with minimum required difference scores of 10% for VAS pain[34] and 10% for a timed locomotor step test, similar to the ALF procedure.[172] This may suggest that the MCIDs described by Bellamy and colleagues[160] are a little high, and that on balance there is evidence to support the assertion that the differences demonstrated in this trial are clinically meaningful.

Chapter 6
Conclusions

This report has described the relative clinical effectiveness and cost-effectiveness of two methods of providing exercise treatment for patients with knee osteoarthritis. The decision to evaluate this particular aspect of treatment in this condition was based on a review of the literature and a desire to evaluate common physiotherapeutic practice. The trial met its aims and objectives, answered the main research questions and provided results that can foster further research. The findings of this trial will have contributed to the accumulated knowledge in this area and provided evidence that may influence clinical practice.

Healthcare implications

In summary, the implications of this trial were clinically significant. The supplementation of a home-based exercise programme with a class-based exercise programme led to small but superior improvement in the supplemented group, improvement that was still evident 12 months after the cessation of the exercise classes. This improvement was mirrored in the quality of life measures used in the economic evaluation, with the group receiving the supplementary programme showing small improvements in QALY scores compared with the home-based programme. The additional cost of this improvement was offset by savings elsewhere, mainly in a reduction in primary care contacts. The supplementary class-based programme was therefore likely to be cost-effective, although there was considerable uncertainty in the analysis.

Both programmes led to an improvement in locomotor function and walking pain, with these improvements being accompanied by short-term improvements in lower limb strength, balance and range of movement. The effect of the treatments on the primary outcome measures of the trial could be confidently generalised to the population of patients with knee osteoarthritis, and revealed that the size of the differential improvement between treatments in ALF and VAS pain scores could be considered clinically significant at post-treatment and follow-up assessments. The size of the treatment effects was generally small, apart from the reduction in pain reported while walking, which was moderate to large. The differential improvement between the two exercise programmes was thought to be due to a combination of physical and psychosocial factors. The supplemented group undertook exercise that required more time to undertake, was more frequently undertaken and was of a higher intensity than the home group. Physical factors such as strength and neuromuscular control were thought to have improved as a result of the greater focus on these activities in the supplemented group. However, the differential improvement in all the physical factors was not maintained over the 12-month review period, whereas the primary outcome improvement remained greater in the supplemented group. The psychosocial benefits of the supplemented programme may have contributed to maintenance of this differential improvement.

Compliance with the home exercise programme was not different between the groups at the 6- and 12-month reviews, although the supplemented group did describe increased physical activity levels. Compliance with a home exercise programme has been shown to be an important factor in the effectiveness of the treatments, but was not influenced by supplementation with an 8-week class-based exercise programme, despite the considerable difference in the intensity of the two treatments. This suggests that the optimal method for providing class-based exercise programmes, to facilitate compliance, has yet to be established and offers an interesting area for exploration.

Recommendations for future research

This investigation has highlighted a number of areas that require further investigation before the optimal method of providing exercise for patients with knee osteoarthritis can be realised. Some of these questions can be addressed using data collected during the course of this investigation, whereas others will require specific investigation via further qualitative and quantitative methods. These questions, in order of priority are listed below.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Would the effect of staging the interventions in the primary care setting influence effectiveness?

The vast majority of patients with osteoarthritis of the knee are managed in the primary care setting. The effectiveness of these interventions needs to be evaluated in this setting, where the beneficial effects of these interventions may have a considerably larger effect on the economic burden of this condition.

How can adherence with home exercise be increased?

Long-term adherence with prescribed home exercise was not significantly improved with the provision of 8 weeks of intensive class-based exercise. Methods of optimising adherence with home exercise programmes need to be established.

What are the factors that led to maintenance of locomotor function improvement while improvements in muscle strength and balance failed to be maintained?

The maintenance of improved locomotor function could not be solely attributed to physical improvement. The psychosocial influences on function in response to exercise provision require further exploration to optimise treatment effects.

Acknowledgements

Material in this report has been published in *Rheumatology* 2004;**43**;514–17 and *Rheumatology* 2004;**43**;880–6, and is reproduced with the kind permission of Oxford University Press/British Society of Rheumatology.

Thanks to the clinical department of Physiotherapy at Manchester Royal Infirmary (MRI) and Rheumatology and Orthopaedic Staff, and the local GPs of the central Manchester area for referring patients to the study.

Thanks also to Dr Darren Clement for designing the trial database, Carol Cooper for maintaining and improving the database, Alex Wilkinson for data inputting and auditing, and Gill Haworth for helping with the organisation and running of the classes.

Finally, thanks to Liz Fenwick at Centre for Health Economics, University of York, for the development of software for CEAC.

Contributions of authors

CJ McCarthy (Research Physiotherapist) coordinated the trial and was the major contributor to the report preparation. PM Mills (Senior Lecturer in Physiotherapy) was lead applicant on the HTA application and was involved in the design of the intervention. R Pullen (Senior Physiotherapist) conducted all interventions. G Richardson (Health Economist) designed the health economy analysis. N Hawkins (Health Economist) contributed towards the health economy analysis. CR Roberts (Senior Lecturer in Medical Statistics) conducted the statistical analysis of the clinical trial data. AJ Silman (Professor of Epidemiology) was the adviser on trial design and conduct. JA Oldham (Professor of Rehabilitation Science) was the supervisor of the trial and the write-up of the report.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

References

1. Brazier JE, Harper R, Munro J, Walters SJ, Snaith ML. Generic and condition-specific outcome measures for people with osteoarthritis of the knee. *Rheumatology (Oxford)* 1999;**38**:870–7.
2. Martin DF. Pathomechanics of knee osteoarthritis. *Med Sci Sports Exerc* 1994;**26**:1429–34.
3. Van Baar ME, Dekker J, Oostendorp RA, Bijl D, Voorn TB, Lemmens JA, *et al*. The effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a randomized clinical trial. *J Rheumatol* 1998;**25**:2432–9.
4. Felson DT. The epidemiology of knee osteoarthritis: results of the Framingham Osteoarthritis Study. *Semin Arthritis Rheum* 1990; **20**:42–50.
5. Creamer P, Lethbridge CM, Hochberg MC. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. *J Rheumatol* 1999;**26**:1785–92.
6. Mankin HJ, Brandt KD, Schulman LE. Workshop on the aetiopathology of osteoarthritis. *J Rheumatol* 1986;**13**:1177–86.
7. Doherty M. Introduction: the nature of osteoarthritis. In Doherty M, editor. *Color atlas and text of osteoarthritis*. London: Wolfe; 1994. pp. 7–14.
8. Carr A. Beyond disability: measuring the social and personal consequences of osteoarthritis. *Osteoarthritis Cartilage* 1999;**7**:230–8.
9. Dieppe PA, Basler HD, Chard P, Croft P, Dixon M, Hurley MV, *et al*. Knee replacement surgery for osteoarthritis: effectiveness, practice, variations, indications and possible determinants of utilization. *Rheumatology* 1999;**38**:73–83.
10. Van Sasse JLCM, Van der Korst JK, Cats A, Valkenburg HA. Comparison of radiological osteoarthritis in a Dutch population with that of 10 other populations. *Ann Rheum Dis* 1989; **48**:271–80.
11. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;**60**:91–7.
12. Sumners MN, Haley WE, Reveille JO, Alarcon GS. Radiographic assessment and psychological variables as predictors of pain and functional impairment in osteoarthritis of the knee or hip. *Arthritis Rheum* 1988;**31**:204–9.
13. Cooper C, Snow S, McAlindon TE, Dieppe PA. Risk factors for the incidence and progression of radiographic osteoarthritis. *Arthritis Rheum* 2000; **43**:995–1000.
14. Marks R, Cantin D. Symptomatic osteoarthritis of the knee: the efficacy of physiotherapy. *Physiotherapy* 1997;**83**:306–12.
15. Wilmoth JR. Demography of longevity: past, present and future trends. *Exp Gerontol* 2000; **35**:1111–29.
16. McCormick A, Fleming D, Charlton J. *Morbidity statistics from general practice: fourth national study 1991–1992*. London: HMSO; 1995.
17. Phillips AM, Goddard NJ, Tomlinson JE. Current techniques in total knee replacement: results of a national survey. *Ann R Coll Surg Engl* 1996; **78**:515–20.
18. Health Care Evaluation Unit. Epidemiology based needs assessment – total hip and knee joint replacements. Bristol: University of Bristol; 1990.
19. Murray CJL, Lopez AD. *The global burden of disease*. Geneva: World Health Organization; 1997.
20. Weinberger M, Tierney WM, Booher P. Common problems experienced by adults with osteoarthritis. *Arthritis Care and Research* 1989; **2**:94–100.
21. Chief Medical Officer of the Department of Health. *On the state of the public health*. London: The Stationery Office; 1996.
22. Office of Population Censuses and Surveys. *Surveys of disability in Great Britain: the prevalence of disability among adults*. Report. London: HMSO; 1988.
23. British Society for Rheumatology/Royal College of Practitioners. *Guidelines: diagnosis and management of osteoarthritis of the hip and knee*. 27th ed. London: RCP Publications; 1993.
24. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, *et al*. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology. *Arthritis Rheum* 1995;**38**:1541–6.
25. Altman RD, Hochberg MC, Moskowitz RW, Schnitzer TJ. Recommendations for the medical management of osteoarthritis of the hip and knee: update 2000. *Arthritis Rheum* 2000;**43**:1905–15.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

26. Mazieres B, Bannwarth B, Dougados M, Lequesne M. EULAR recommendations for the management of knee osteoarthritis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials. *Joint Bone Spine* 2001; **68**:231–40.

27. Barclay J. *In good hands: the history of the Chartered Society of Physiotherapy*. Oxford: Butterworth-Heinemann; 1994.

28. Tallon D, Chard JA, Dieppe PA. Exploring the priorities of patients with osteoarthritis of the knee. *Arthritis Care and Research* 2000;**13**:312–19.

29. Ross F, Triggs E, Cadbury H, Axford J, Victor C. Evaluation of education for people with osteoarthritis of the knee: recruitment and retention issues in study design. *Nurse Researcher* 1998;**6**:49–59.

30. Mazzuca SA, Brandt KD, Katz BP, Chambers M, Byrd D, Hanna M. Effects of self care education on the health status of inner-city patients with osteoarthritis of the knee. *Arthritis Rheum* 1997; **40**:1466–74.

31. Frost H, Lamb SE, Robertson S. A randomized controlled trial of exercise to improve mobility and function after elective knee arthroplasty. Feasibility, results and methodological difficulties. *Clin Rehabil* 2002;**16**:200–9.

32. Barlow JH, Turner AP, Wright CC. Sharing, caring and learning to take control: self-management training for people with arthritis. *Psychology Health and Medicine* 1998;**3**:387–93.

33. Barlow JH, Turner AP, Wright CC. Long-term outcomes of an arthritis self-management programme. *British Journal of Rheumatology* 1998; **37**:1315–19.

34. Hopman-Rock M, Westhoff MH. The effects of a health educational and exercise program for older adults with osteoarthritis of the hip or knee. *J Rheumatol* 2000;**27**:1947–54.

35. Arthritis Research Campaign. *Physiotherapy and arthritis*. London: ARC, 1997.

36. Clarke AK. Effectiveness of rehabilitation in arthritis. *Clin Rehabil* 1999;**13**(1 Suppl):51–62.

37. Hurley MV, Scott DL. Improvements in quadriceps sensorimotor function and disability of patients with knee osteoarthritis following a clinically practicable exercise regime. *British Journal of Rheumatology* 1998;**37**:1181–7.

38. Iverson MD, Fossel AH, Daltroy LH. Rheumatologist–patient communication about exercise and physical therapy in the management of rheumatoid arthritis. *Arthritis Care and Research* 1999;**12**:180–92.

39. Arthritis Research Campaign. *An information booklet: osteoarthritis of the knee*. London: ARC; 1998.

40. Altman RD, Asch E, Bloch DA, Borenstein D, Brandt K. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum* 1986;**29**:1039–49.

41. Chiarello CM, Savidge R. Interrater reliability of the Cybex EDI-320 and fluid goniometer in normals and patients with low back pain. *Arch Phys Med Rehabil* 1993;**74**:32–7.

42. Dieppe PA. Osteoarthritis: time to shift the paradigm. *BMJ* 1999;**318**:1299–300.

43. Lankhorst GJ, Van de Stadt RJ, Van der Korst JK. The relationships of functional capacity, pain and isometric and isokinetic torque in osteoarthritis of the knee. *Scand J Rehabil Med* 1985;**17**:167–72.

44. Berry MJ, Brubaker PH, O'Toole M, Rejeski WJ, Soberman J, Ribisl PM, *et al*. Estimation of VO_2 in older individuals with osteoarthritis of the knee and cardiovascular disease. *Med Sci Sports Exerc* 1996;**28**:808–14.

45. Messier SP, Loeser RF, Hoover JL, Semble EL, Wise CM. Osteoarthritis of the knee: effects on gait, strength, and flexibility. *Arch Phys Med Rehabil* 1992;**73**:29–36.

46. Ettinger WH, Afable RF. Physical disability from knee osteoarthritis: the role of exercise as an intervention. *Med Sci Sports Exerc* 1994; **26**:1435–40.

47. McCubbin JA. Resistance training for persons with arthritis. *Rheum Dis Clin North Am* 1990;**16**:931–43.

48. Keefe AX, Hageman PA, Dahlberg L. Pain in arthritis and musculoskeletal disorders: the role of coping skills, training and exercise interventions. *J Orthop Sports Phys Ther* 1996;**24**:279–90.

49. Harkcom TM, Lampman RM, Banwell BF, Castor CW. Therapeutic value of graded aerobic exercise training in rheumatoid arthritis. *Arthritis Rheum* 1985;**28**:32–9.

50. Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. *Arthritis Rheum* 1989;**32**:1396–405.

51. Ekdahl C, Andersson G, Moritz V, Svensson B. Dynamic versus static training in patients with rheumatoid arthritis. *Scand J Rheumatol* 1990; **19**:17–26.

52. Fisher NM, Pendergast DR, Gresham GE, Calkins E. Muscle rehabilitation: its effect on muscular and functional performance of patients with knee osteoarthritis. *Arch Phys Med Rehabil* 1991;**72**:367–74.

53. Fisher NM, Gresham G, Pendergast DR. Effects of a quantitative progressive rehabilitation program applied unilaterally to the osteoarthritic knee. *Arch Phys Med Rehabil* 1993;**74**:1319–26.

54. Fisher NM, Kame VD Jr, Rouse L, Pendergast DR. Quantitative evaluation of a home exercise program on muscle and functional capacity of patients with osteoarthritis. *Am J Phys Med Rehabil* 1994;**73**:413–20.

55. Fisher NM, Pendergast DR. Effects of a muscle exercise program on exercise capacity in subjects with osteoarthritis. *Arch Phys Med Rehabil* 1994; **75**:792–7.

56. Fisher NM, White SC, Yack HJ, Smolinski RJ, Pendergast DR. Muscle function and gait in patients with knee osteoarthritis before and after muscle rehabilitation. *Disabil Rehabil* 1997; **19**:47–55.

57. Ettinger WH, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, *et al*. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). *JAMA* 1997;**277**:25–31.

58. Rogind H, Bibow NB, Jensen B, Moller HC, Frimodt MH, Bliddal H. The effects of a physical training program on patients with osteoarthritis of the knees. *Arch Phys Med Rehabil* 1998;**79**:1421–7.

59. Callaghan MJ, Oldham JA, Hunt J. An evaluation of exercise regimes for patients with osteoarthritis of the knee: a single-blind randomized controlled trial. *Clin Rehabil* 1995;**9**:213–18.

60. McCarthy CJ, Oldham JA. The effectiveness of exercise in the treatment of osteoarthritic knees: a critical review. *Physical Therapy Reviews* 1999; **4:**241–50.

61. Walker CR, Myles C, Nutton R, Rowe P. Movement of the knee in osteoarthritis. The use of electrogoniometry to assess function. *J Bone Joint Surg Br* 2001;**83**:195–8.

62. Chalmers I. Unbiased, relevant and reliable assessments in health care. *BMJ* 1998;**317**:1167–8.

63. Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. *BMJ* 1996;**313**:570–1.

64. Wakefield A. Evidence-based physiotherapy: the case for pragmatic randomised controlled trials. *Physiotherapy* 2000;**86**:394–6.

65. Maitland GD. *Peripheral manipulation*. 3rd ed. London: Butterworth-Heinemann; 1991.

66. Bellamy N, Klestov A, Muirden K, Kuhnert P, Martin N. Perceptual variation in categorizing individuals according to the American College of Rheumatology classification criteria for hand, knee and hip osteoarthritis (OA): observations based on an Australian twin registry study of OA. *J Rheumatol* 1999;**26**:2654–8.

67. Altman RD, Alaranta H, Bloch DA, Borenstein D, Brandt K. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum* 1991; **34**:505–14.

68. Sim J, Wright C. *Research in health care: concepts, designs and methods*. Cheltenham: Stanley Thornes; 2000.

69. Elashoff J. *nQuery Advisor® version 3.0. User's guide*. Los Angeles, CA: Dixon Associates; 1999.

70. Friedman LM, Furberg CD, DeMets DL. *Fundamentals of clinical trials*. 3rd ed. New York: Springer; 2001.

71. Roberts C, Torgerson J. Understanding controlled trials: baseline imbalance in randomised controlled trials. *BMJ* 1999;**319**:185.

72. Davis MA, Ettinger-WH J, Neuhaus JM, Hauck WW. Sex differences in osteoarthritis of the knee. The role of obesity. *Am J Epidemiol* 1988; **127**:1019–30.

73. Thomas JR, Nelson JK. Experimental research. In: Thomas JR, Nelson JK, editors. *Research methods in physical activity*. Champaign, IL: Human Kinetics Books; 1990. pp. 297–321.

74. Davis MA, Ettinger WH, Neuhaus JM, Mallon KP. Knee osteoarthritis and physical functioning: evidence from the NHANES I epidemiologic followup study. *J Rheumatol* 1991;**18**:591–8.

75. Bellamy N. *Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index: user's guide*. London, Ontario: University of Western Ontario; 1996.

76. Wijlhuizen GJ, Ooijendijk W. Measuring disability, the agreement between self evaluation and observation of performance. *Disabil Rehabil* 1999; **21**:61–7.

77. Haghani H, Marks R. Relationship between maximal isometric knee extensor and flexor strength measures, age and walking speed of healthy men and women ages 18–74. *Physiotherapy Canada* 2000;**34**:33–8.

78. Podsiadlo D, Richardson S. The timed 'up and go': a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;**39**:142–8.

79. Steultjens MM, Dekker J, van BM, Oostendorp RB, Bijlsma JJ. Internal consistency and validity of an observational method for assessing disability in mobility in patients with osteoarthritis. *Arthritis Care and Research* 1999;**12**:19–25.

80. Bussman JBJ, Stam HJ. Techniques for the measurement and assessment of mobility in rehabilitation: a theoretical approach. *Clin Rehabil* 1998;**12**:455–64.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

81. Myers AM, Holliday PJ, Harvey KA, Hutchinson KS. Functional performance measures: are they superior to self-assessments? *J Gerontol A Biol Sci Med Sci* 1993;**48**:M196–206.

82. Watson D. Health complaints, stress and distress: exploring the central role of negative affectivity. *Psychol Rev* 1989;**96**:234–54.

83. Bohannon RW. Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants. *Age Aging* 1997;**26**:15–19.

84. Pine ZM, Gurland B, Chren MM. Report of having slowed down: Evidence for the validity of a new way to enquire about mild disability in elders. *J Gerontol A Biol Sci Med Sci* 2000;**55**:M378–83.

85. Messier SP, Ettinger WH Jr, Doyle DV, Morgan T, James MK, O'Toole M, *et al*. Obesity: effects on gait in an osteoarthritic population. *Journal of Applied Biomechanics* 1996;**12**:161–72.

86. Youdas JW, Atwood AL, Harris-Lowe MO, Stiller TL, Egan KS, Therneau TM. Measurements of temporal aspects of gait obtained with a multimemory stopwatch in persons with gait impairments. *J Orthop Sports Phys Ther* 2000; **30**:279–86.

87. Marks R. Reliability and validity of self-paced walking time measures for knee osteoarthritis. *Arthritis Care and Research* 1994;**7**:50–3.

88. Fransen M, Crosbie J, Edmonds J. Reliability of gait measurements in people with osteoarthritis of the knee. *Phys Ther* 1997;**77**:944–53.

89. Kerrigan DC, Todd MK, Lipsitz LA, Collins JJ. Biomechanical gait alterations independent of speed in healthy elderly: evidence for specific impairments. *Arch Phys Med Rehabil* 1998; **79**:317–22.

90. Howe TE, Oldham JA. Functional tests in elderly osteoarthritic subjects: variability of performance. *Nursing Standard* 1995;**9**:35–8.

91. Hirokawa S. Normal gait characteristics under temporal and distance constraints. *J Biomech Eng* 1989;**11**:449–56.

92. Sharma L, Felson DT. Studying how osteoarthritis causes disability: nothing is simple. *J Rheumatol* 1998;**25**:1–4.

93. Lequesne MG, Brandt K, Bellamy N. Guidelines for testing slow acting drugs in osteoarthritis. *J Rheumatol* 1994;**21**(suppl 41):65–73.

94. Andriacchi TP, Andersson GB, Fermier RW, Stern D, Galante JO. A study of lower-limb mechanics during stair-climbing. *J Bone Joint Surg Am* 1980;**62**:749–57.

95. Bassey EJ, Fiatarone MA, O'Neill EF, Kelly M, Evans WJ. Leg extension power and functional performance in very old men and women. *Clin Sci* 1992;**82**:321–7.

96. Oldham JA, Howe TE. Applicability of quadriceps muscle strength as an indicator of functional performance in elderly osteoarthritic subjects. *Clinical Effectiveness in Nursing* 1998;**2**:39–40.

97. Jette AM, Jette DU, Ng J, Plotkin DJ, Bach MA. Are performance-based measures sufficiently reliable for use in multicenter trials? Musculoskeletal Impairment (MSI) Study Group. *J Gerontol A Biol Sci Med Sci* 1999;**54**(1):M3–6.

98. Freter SH, Fruchter N. Relationship between timed 'up and go' and gait time in an elderly orthopaedic rehabilitation population. *Clin Rehabil* 2000;**14**(96):101.

99. Samson MM, Meeuwsen IAEB, Crowe A, Dessens JAG, Duursma SA, Verhaar HJJ. Relationships between physical performance measures, age, height and body weight in healthy adults. *Age Ageing* 2000;**29**:235–42.

100. Shumway-Cook A, Brauer S, Wollacott M. Predicting the probability for falls in community-dwelling older adults using the timed 'up and go' test. *Phys Ther* 2000;**80**:896–903.

101. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. *Pain* 1983;**16**:87–101.

102. Tiplady B, Jackson SHD, Maskrey VM, Swift CG. Validity and sensitivity of visual analogue scales in young and older healthy subjects. *Age Ageing* 1998; **27**:63–6.

103. Flandry F, Hunt JP, Terry GC, Hughston JC. Analysis of subjective knee complaints using visual analog scales. *Am J Sports Med* 1991;**19**:112–18.

104. Melzack R. The McGill pain questionnaire: major properties and scoring methods. *Pain* 1975; **1**:277–99.

105. Bellamy N. Outcome measurement on osteoarthritis clinical trials. *J Rheumatol* 1995; **22**(suppl 43):49–51.

106. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988; **15**:1833–40.

107. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes following total hip or knee arthroplasty in osteoarthritis. *J Orthop Rheumatol* 1988;**1**:95–108.

108. Davies GM, Watson DJ, Bellamy N. Comparison of the responsiveness and relative effect size of the

Western Ontario and McMaster Universities Osteoarthritis Index and the Short-Form Medical Outcomes Study Survey in a randomized, clinical trial of osteoarthritis patients. *Arthritis Care and Research* 1999;**12**:172–9.

109. Lequesne M. Indices of severity and disease activity for osteoarthritis. *Semin Arthritis Rheum* 1991;**20**(6 Suppl 2):48–54.

110. Dougados M, LeClaire P, Van de Heijde D, Bloch DA, Bellamy N, Altman RD. A report of the Osteoarthritis Research Society International Standing Committee for clinical trials response criteria initiative. *Osteoarthritis Cartilage* 2000; **8**:395–403.

111. Barr S, Bellamy N, Buchanan WW, Chalmers A, Ford PM, Kean WF, *et al*. A comparative study of signal versus aggregate methods of outcome measurement based on the WOMAC Osteoarthritis Index. Western Ontario and McMaster Universities Osteoarthritis Index. *J Rheumatol* 1994;**21**:2106–12.

112. Ware JE, Snow K, Kosinski M, Gandek B. *SF-36 health survey manual and interpretation guide*. Boston, MA: New England Medical Center; 1993.

113. Hemingway H, Stafford M, Stansfield S, Shipley M, Marmot M. Is the SF-36 a valid measure of change in population health? Results from the Whitehall II study. *BMJ* 1997;**315**:1273–9.

114. Hawker G, Melfi C, Paul J, Green R, Bombardier C. Comparison of a generic (SF-36) and a disease specific (WOMAC) (Western Ontario and McMaster Universities Osteoarthritis Index) instrument in the measurement of outcomes after knee replacement surgery. *J Rheumatol* 1995; **22**:1193–6.

115. Kosinski M, Keller SD, Hatoum HT, Kong SX, Ware JE. The SF-36 Health Survey as a generic outcome measure in clinical trials of patients with osteoarthritis and rheumatoid arthritis: tests of data quality, scaling assumptions and score reliability. *Med Care* 1999;**37**(5):MS10–22.

116. Fransen M, Edmonds J. Reliability and validity of the EuroQol in patients with osteoarthritis of the knee. *Rheumatology (Oxford)* 1999;**38**:807–13.

117. Hurst NP, Jobanputra P, Hunter M, Lambert M, Lochhead A, Brown H. Validity of Euroqol – a generic health status instrument – in patients with rheumatoid arthritis. Economic and Health Outcomes Research Group. *British Journal of Rheumatology* 1994;**33**:655–62.

118. Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). *British Journal of Rheumatology* 1997;**36**:551–9.

119. Wolfe F, Hawley DJ. Measurement of the quality of life in rheumatic disorders using the EuroQol. *British Journal of Rheumatology* 1997;**36**:786–93.

120. Centre for Health Economics. *EuroQol EQ-5D: user guide. Version B*. York. Centre for Health Economics, University of York; 1998.

121. Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. *Rheum Dis Clin North Am* 1999;**25**:283–98,vi.

122. Marks R. The effect of isometric quadriceps strength training in mid-range for osteoarthritis of the knee. *Arthritis Care and Research* 1993;**6**:52–6.

123. Marks R. The effects of 16 months of angle-specific isometric strengthening exercises in midrange on torque of the knee extensor muscles in osteoarthritis of the knee: a case study. *J Orthop Sports Phys Ther* 1994;**20**:103–9.

124. Rutherford OM, Jones DA. Contractile properties and fatigability of the human adductor pollicis and first doral interosseous: a comparison of the effects of two chronic stimulation patterns. *J Neurol Sci* 1988;**85**:319–31.

125. Schmitz R, Arnold BL. Intertester and intratester reliability of a dynamic balance protocol using the Biodex Stability system. *Journal of Sports Rehabilitation* 1998;**7**:95–101.

126. Thapa PB, Gideon P, Brockman KG, Fought RL, Ray WA. Clinical and biomechanical measures of balance as fall predictors in ambulatory nursing home residents. *J Gerontol A Biol Sci Med Sci* 1996; **51**:M239–46.

127. Lane NE. Exercise: a cause of osteoarthritis. *J Rheumatol Suppl* 1995;**43**:3–6.

128. Pincivero D, Lephart SM. Learning effects and reliability of the biodex stability system. *Journal of Athletic Training* 1995;**30**(Suppl):S30–5.

129. Kirby RL, Price NA, MacLeod DA. The influence of foot position on standing balance. *J Biomech* 1987;**20**:423–7.

130. Coates H, King A. *The patient assessment*. Edinburgh: Churchill Livingstone; 1982.

131. Watkins MA, Riddle DL, Lamb RL, Personius WJ. Reliability of goniometric measurements and visual estimates of knee range of motion obtained in a clinical setting. *Phys Ther* 1991;**71**:15–21.

132. Gogia PP, Braatz JH, Rose S, Norton BJ. Reliability and validity of goniometric measurements at the knee. *Phys Ther* 1987; **67**:192–5.

133. Campbell R, Evans M, Tucker B, Quilty B, Donovan JL. Why don't patients do their exercises? Understanding non-compliance with physiotherapy in patients with osteoarthritis of the knee. *J Epidemiol Community Health* 2001;**55**:132–8.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

134. Seckin U, Gunduz S, Borman P, Akyuz M. Evaluation of the compliance to exercise therapy in patients with knee osteoarthritis. *Journal of Back and Musculoskeletal Rehabilitation* 2000;**14**:113–15.

135. Sluijs EM, Kok GJK, Zee J. Correlates of exercise compliance in physical therapy. *Phys Ther* 1993; **73**:771–86.

136. Vitolins M, Rand C, Rapp S, Ribisl P, Sevick M. Measuring adherence to behavioral and medical interventions. *Control Clin Trials* 2000;**21**:188–94S.

137. Stratford PW, Goldsmith CH. Use of the standard error as a reliability index of interest: an applied example using elbow flexor strength data. *Phys Ther* 1997;**77**:745–50.

138. Campbell DT, Stanley JC. *Experimental and quasi-experimental designs for research*. Chicago, IL: Rand McNally; 1963.

139. Borjesson M, Robertson E, Weidenhielm L, Mattsson E, Olsson E. Physiotherapy in knee osteoarthrosis: effect on pain and walking. *Physiother Res Int* 1996;**1**:89–97.

140. Minor MA. Exercise in the management of osteoarthritis of the knee and hip. *Arthritis Care and Research* 1994;**7**:198–204.

141. Kavounoudias A, Gilhodes JC, Roll R, Roll JP. From balance regulation to body orientation: two goals for muscle proprioceptive information processing? *Exp Brain Res* 1999;**124**:80–8.

142. Brandt K. The importance of nonpharmacological approaches in management of osteoarthritis. *Am J Med* 1998;**105**(1B):39–44S.

143. Singh SJ, Morgan MDL, Hardman AE. *The shuttle walking test*. Loughborough: Loughborough University; 1992.

144. Diggle PJ, Liang KY, Zeger SL. *Analysis of longitudinal data*. Oxford: Oxford Scientific Publications; 1994.

145. Everitt BS, Pickles A. *Statistical aspects of the design and analysis of clinical trials*. London: Imperial College Press; 1999.

146. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *JAMA* 2001;**285**:1987–91.

147. McCullagh P, Nelder JA. *Generalized linear models*. 2nd ed. London: Chapman & Hall; 1989.

148. Goldstein H. *Multilevel statistical models*. London: Arnold; 1995.

149. Netten A, Curtis L. *Unit costs of health and social care 2000*. University of Kent, Canterbury: Personal Social Services Research Unit; 2000.

150. Chartered Institute of Public Finance and Accountancy. *Health services financial database*. London: CIPFA; 2001.

151. EuroQol Group. EuroQol – a new facility for the measurement of health related quality of life. *Health Policy* 1990;**19**:199–208.

152. Dolan P, Gudex C, Kind P, Williams A. *A social tariff for EuroQol: results from a UK general population survey*. Discussion Paper 138. York: Centre for Health Economics, University of York; 1995.

153. Rubin DM, Stern HS, Vehovar V. Handling 'don't know' survey responses: the case of Slovenian plebiscite. *Journal of the American Statistical Association* 1995;**90**:822–8.

154. Curran D, Bacchi M, Hsu Schmitz SF. Identifying the types of missingness in quality of life data from clinical trials. *Stat Med* 1998;**17**:547–59.

155. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998; **18**:S68–80.

156. Tambour M, Zethraeus N. A note on confidence intervals in cost-effectiveness analysis. *Int J Technol Assess Health Care* 1998;**14**:467–71.

157. Fenwick E, Claxton K, Sculpher M, Briggs A. *Improving efficiency and relevance of health technology assessment: the role of iterative decision analytic modelling*. Discussion Paper 179. York: Centre for Health Economics, University of York; 2001.

158. Lord J, Victor C, Littlejohns P, Ross FM, Axford JS. Economic evaluation of a primary care based education programme for patients with osteoarthritis of the knee. *Health Technol Assess* 1999;**3**(23).

159. Briggs A, O'Brien B. The death of cost-minimisation analysis? *Health Econ* 2001;**10**:179–84.

160. Bellamy N, Carette S, Ford PM, Kean WF, Le Riche NGH, Lussier A, *et al*. Osteoarthritis antirheumatic drug trials, III. Setting the Delta for clinical trials – results of a consensus development (Delphi) exercise. *J Rheumatol* 1992;**19**:451–7.

161. Fransen M, Crosbie J, Edmonds J. Physical therapy is effective for patients with osteoarthritis of the knee: a randomised controlled clinical trial. *Rheumatology* 2001;**28**:156–64.

162. O'Reilly SC, Muir KR, Doherty M. Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. *Ann Rheum Dis* 1999;**58**:15–19.

163. Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual therapy and exercise in osteoarthritis of the knee. A randomised controlled trial. *Ann Intern Med* 2000;**132**:173–81.

164. Baker K, Nelson JK, Felson DT, Layne JE, Sarno R, Roubenoff R. The efficacy of home-based exercise progressive strength training in older adults with knee osteoarthritis: a randomised controlled trial. *J Rheumatol* 2001;**28**:1655–65.

165. Jefferson RJ, Collins JJ, Whittle MW, Radin EL. The role of the quadriceps in controlling impulse forces around heel strike. *Proc Inst Mech Eng* 1990; **204**:21–8.

166. Voloshin AS, Mizrahi J, Verbitsky O, Isakov E. Dynamic loading on the human musculoskeletal system – effect of fatigue. *Clin Biomech* 1998; **13**:515–20.

167. Slemenda C, Brandt KD, Heilman MS, Mazzuca SA, Braunstein EM, Katz BP, *et al*. Quadriceps weakness and osteoarthritis of the knee. *Ann Intern Med* 1997;**127**:97–104.

168. Hurwitz DE, Ryals AR, Block JA, Sharma L, Schnitzer TJ, Andriacchi TP. Knee pain and joint loading in subjects with osteoarthritis of the knee. *J Orthop Res* 2000;**18**:572–9.

169. Evans WJ. Exercise guidelines for the elderly. *Med Sci Sports Exerc* 1998;**31**:12–17.

170. Chamberlain MA, Care G, Harfield B. Physiotherapy in osteoarthrosis of the knees. A controlled trial of hospital versus home exercises. *Int Rehabil Med* 1982;**4**:101–6.

171. Van Baar ME. *Effectiveness of exercise therapy in osteoarthritis of the hip or knee*. Utrecht: Utrecht University; 1998.

172. Petrella RJ, Bartha C. Home based exercise therapy for older patients with knee osteoarthritis: a randomised clinical trial. *Rheumatology* 2000; **27**:2215–21.

173. Friedrich M, Gittler G, Halberstadt Y, Cermak T, Heiller I. Combined exercise and motivation program: effect on the compliance and level of disability of patients with chronic low back pain: A randomised controlled trial. *Arch Phys Med Rehabil* 1998;**79**:475–87.

174. Marks R. Peripheral articular mechanisms in pain production in osteoarthritis. *Australian Journal Physiotherapy* 1992;**38**:289–98.

175. Marks R. Muscles as a pathogenic factor in osteoarthritis. *Physiotherapy Canada* 1993;**45**:251–9.

176. O'Reilly SC, Jones A, Doherty M. Muscle weakness in osteoarthritis. *Curr Opin Rheumatol* 1997; **9**:259–62.

177. Messier SP, Royer TD, Craven TE, O'Toole M, Burns R, Ettinger WH. Long-term exercise and its effect on balance in older osteoarthritic adults: results from the Fitness, Arthritis and Seniors trial (FAST). *J Am Geriatr Soc* 2000;**48**:131–8.

178. Scarborough DM, Krebs DE, Harris BA. Quadriceps muscle strength and dynamic stability in elderly persons. *Gait Posture* 1999;**10**:10–20.

179. Sharma L, Hayes KW, Felson DT, Buchanan TS, Kirwan MG, Lou C, *et al*. Does laxity alter the relationship between strength and physical function in knee osteoarthritis? *Arthritis Rheum* 1999;**42**:25–32.

180. American College of Sports Medicine. Guidelines for graded exercise testing and exercise prescription. *Med Sci Sports Exerc* 1991;**22**:265–74.

181. Sauvage-LR J, Myklebust BM, Crow PJ, Novak S, Millington P, Hoffman MD, *et al*. A clinical trial of strengthening and aerobic exercise to improve gait and balance in elderly male nursing home residents. *Am J Phys Med Rehabil* 1992;**71**:333–42.

182. Hytonen M, Pyykko I, Aalto H, Starck J. Postural control and age. *Acta Otolaryngol* 1993;**113**:119–22.

183. Minor MA, Hewett JE, Webel RR, Dreisinger TE, Kay DR. Exercise tolerance and disease related measures in patients with rheumatoid arthritis and osteoarthritis. *J Rheumatol* 1988;**15**:905–11.

184. Creamer P, Lethbridge-Cejku M, Hochberg M. Factors associated with functional impairment in symptomatic knee osteoarthritis. *Rheumatology* 2000;**29**:490–6.

185. Dexter PA. Joint exercises in elderly persons with symptomatic osteoarthritis of the hip or knee. Performance patterns, medical support patterns, and the relationship between exercising and medical care. *Arthritis Care and Research* 1992; **5**:36–41.

186. Ferri M, Brooks D, Goldstein RS. Compliance with treatment – an ongoing concern. *Physiotherapy Canada* 1998;**3**:286–90.

187. Thomas JR, Nelson JK. *Research methods in physical activity*. 2nd ed. Champaign, IL: Human Kinetic Books; 1990.

188. Wells G, Beaton D, Shea B, Boers M, Simon L, Strand V, *et al*. Minimal clinically important differences: review of methods. *J Rheumatol* 2001; **28**:406–12.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Appendix 1

Compliance questionnaire

PLEASE ANSWER THE FOLLOWING QUESTIONS HONESTLY. THE ANSWERS YOU GIVE WILL NOT AFFECT ANY FURTHER TREATMENT YOU MAY RECEIVE.

1. IN THE LAST MONTH, HOW MANY TIMES A WEEK HAVE YOU BEEN DOING THE EXERCISES SHOWN TO YOU BY THE PHYSIOTHERAPIST?

   a. Never. ☐
   b. Once a week. ☐
   c. Twice a week. ☐
   d. Three times a week. ☐
   e. Four times a week. ☐
   f. Five times a weeek. ☐
   g. Six times a week. ☐
   h. Every day. ☐
   i. Twice a day. ☐

2. WHEN YOU DO YOUR HOME EXERCISES, HOW LONG DO YOU SPEND DOING THEM?

   a. Less than five minutes. ☐
   b. Less than ten minutes. ☐
   c. Less than fifteen minutes. ☐
   d. Less than half an hour. ☐
   e. More than half an hour. ☐

3. IF YOU HAVE STOPPED DOING THE EXERCISES, HOW LONG AGO DID YOU STOP?

   a. I have not stopped. ☐
   b. Less than a week ago. ☐
   c. Less than a month ago. ☐
   d. If more than a month ago please note how many months ago. …….

4. HAS YOUR PHYSICAL ACTIVITY LEVEL –

   a. Gone Up ☐
   b. Gone Down ☐
   c. Stayed the same ☐

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Appendix 2

Educational information and advice presented to patients

Education information

What is osteoarthritis?

What causes osteoarthritis?

Effects of gender, sport, weight, lifestyle, etc.

What are the treatment options for osteoarthritis?

What has physiotherapy to offer?

What are the benefits of exercise for knee osteoarthritis?

The importance of doing exercises.

Advice for both groups of patients with knee osteoarthritis

Reduce the stress on your joints by keeping your weight to a reasonable level.

Walk or stand within the limits of your pain.

Use a walking stick if you need to reduce stress on your joints.

Balance work and rest to avoid any undue fatigue.

Rest for 5–10 minutes in every hour of prolonged physical activity.

Adapt the chair you regularly sit in so that your hips and knees are at a right angle; this will make it easier for you to stand up and sit down.

Avoid the same knee posture for longer than 30 minutes at a time.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Appendix 3

Home exercise sheet

Daily Home Exercises

STRETCHES Do these stretches, three times on each leg.

HIP. With one foot in front of the other gently "lunge" forward onto your front foot. You should feel a slight stretch on your back leg.

ANKLES. Hold onto a work surface or table and without letting your heels come off the floor gently "dip" downwards until you feel a gentle stretch around your ankles.

1. BALANCE.

Stand next to your work surface or table and lift one foot off the floor slightly. Bend your knee slightly. Balance for as long as you can on one foot. When you lose your balance stand on both feet for a few seconds and then balance on the other foot.

Do this for two minutes.

2. EXERCISES.

In standing tighten your thigh muscles as tight as you can.

Hold for ..... seconds. Do this three times.

Sit down on a kitchen or dining room chair. Stand half the way up and hold your bottom 10 inches off the chair.

Hold this for ..... seconds. Do this three times.

Gently go from sitting to standing and back down again. Do this as smoothly as you can.

Do this ..... times daily.

Sitting on a chair, slowly straighten your leg out in front of you.

Hold this for ..... seconds. Do this ten times daily.

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol

Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford

Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine

Dr Jeffrey Aronson
Reader in Clinical Pharmacology, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

Professor Ann Bowling, Professor of Health Services Research, Primary Care and Population Studies, University College London

Professor Andrew Bradbury, Professor of Vascular Surgery, Department of Vascular Surgery, Birmingham Heartlands Hospital

Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health & Related Research, University of Sheffield

Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York

Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen

Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Peter Jones, Head of Department, University Department of Psychiatry, University of Cambridge

Professor Sallie Lamb, Research Professor in Physiotherapy/Co-Director, Interdisciplinary Research Centre in Health, Coventry University

Professor Julian Little, Professor of Epidemiology, Department of Medicine and Therapeutics, University of Aberdeen

Professor Stuart Logan, Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter & Plymouth

Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol

Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Professor Mark Sculpher, Professor of Health Economics, Centre for Health Economics, Institute for Research in the Social Services, University of York

Professor Martin Severs, Professor in Elderly Health Care, Portsmouth Institute of Medicine

Dr Jonathan Shapiro, Senior Fellow, Health Services Management Centre, Birmingham

Ms Kate Thomas, Deputy Director, Medical Care Research Unit, University of Sheffield

Professor Simon G Thompson, Director, MRC Biostatistics Unit, Institute of Public Health, Cambridge

Ms Sue Ziebland, Senior Research Fellow, Cancer Research UK, University of Oxford

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

© Queen's Printer and Controller of HMSO 2004. All rights reserved.

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Dr John Fielding, Consultant Radiologist, Radiology Department, Royal Shrewsbury Hospital

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), Department of Health, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre

Professor Imti Choonara, Professor in Child Health, University of Nottingham, Derbyshire Children's Hospital

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Stan Kaye, Professor of Medical Oncology, Consultant in Medical Oncology/Drug Development, The Royal Marsden Hospital

Ms Barbara Meredith, Project Manager Clinical Guidelines, Patient Involvement Unit, NICE

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Dr Aileen Clarke, Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, Institute of Community Health Sciences, Queen Mary, University of London

Mr Matthew William Cooke, Senior Clinical Lecturer and Honorary Consultant, Emergency Department, University of Warwick, Coventry & Warwickshire NHS Trust, Division of Health in the Community, Centre for Primary Health Care Studies, Coventry

Dr Carl E Counsell, Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of Orthopaedic Surgery, South Tees Hospital NHS Trust

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint

Ms Maryann L. Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Professor James Neilson, Professor of Obstetrics and Gynaecology, Dept of Obstetrics and Gynaecology, University of Liverpool, Liverpool Women's Hospital

Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust

Dr Vimal Sharma, Consultant Psychiatrist & Hon Snr Lecturer, Mental Health Resource Centre, Victoria Central Hospital, Wirrall

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns,
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Mary Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Stephen Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum,
Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs,
Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss,
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Jon Nicholl,
Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick,
National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry, University Mental Health Group, Royal South Hants Hospital, Southampton

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge,
Director, College of Health, London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278