The cost-effectiveness of a home-based exercise programme for the treatment of knee pain in the community

by

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April 2001

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Abstract

Objectives:

- To determine the prevalence of knee pain in the population aged ≥45 years.
- To determine the benefit or otherwise of regular home exercise and telephone contact in reducing the burden of knee pain in the community.
- To determine the economic burden of knee pain from a societal perspective.
- To determine the cost-effectiveness and cost-utility of the compared interventions.

Design: An initial postal questionnaire regarding knee pain was sent to 9296 individuals aged ≥45 years registered with two large general practices in Nottingham. This was followed by a two-year, single-blind, randomised factorial trial. Treatment arms included: exercise therapy, telephone social support, a placebo health food product and no intervention. Economic data were collected prospectively alongside the trial. Analysis was conducted on an intent-to-treat basis.

Primary outcome: Self-reported knee pain at 24 months. This was assessed using the Western Ontario MacMaster's Universities Osteoarthritis Index (WOMAC) – a knee specific questionnaire.

Results: The postal questionnaire was returned by 65% of the study population. The prevalence of self-reported knee pain in the community in those aged ≥45 years was 32% (35% in females and 28% in males). Costs incurred during the 6-month period prior to randomisation showed medical

costs for the treatment of knee pain to be 7% of total medical costs and 11% of primary care costs. Annual societal costs were estimated to be £48 per person.

The intervention study demonstrated that a simple, home-exercise programme could reduce self-reported knee pain, knee stiffness and knee related physical disability after 24 months ($p=<0.001$, 0.01 and <0.001 respectively). Effect sizes were modest, but improvements were incremental to normal care. The number needed to treat (NNT) in order to achieve a $\geq$ 50% reduction in pain at 24 months for individuals allocated to the exercise programme was between 8 and 13. Neither telephone contact nor the placebo dolomite tablet contributed significantly to the observed reduction in pain.

The cost per person of delivering the two-year exercise programme was £113. Analysis of GP records revealed no change in medical costs during the trial. Cost-effectiveness analysis suggested that the cost per unit change on the WOMAC pain scale was £108. The cost-effectiveness of achieving a $\geq$ 50% reduction in pain in a single individual (based on NNT figures) was £1,012.

Conclusion: Knee pain is common in the general UK population aged $\geq$45 years and incurs an estimated cost of £218 to £350 million per annum (excluding indirect costs) in 1996 prices. The burden of knee pain could be reduced by the implementation of a cost-effective primary care-based exercise programme, although such improvements are likely to be modest.

Abbreviations

Δ	Change
ACR	American College of Rheumatology
ASMP	Arthritis self management program
AUC	Area under the curve
BMI	Body mass index
BNF	British National Formulary
C.I.	Confidence interval
COI	Cost-of-illness
EuroQol	European Quality of Life Questionnaire
GI	Gastro-intestinal
GNP	Gross national product
GP	General practitioner
HAD	Hospital Anxiety and Depression Questionnaire
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ITT	Intent-to-treat
KgF	Kilogram force
MVC	Maximum voluntary contraction
N	Newton
NNT	Number needed to treat
NSAID	Non-steroidal anti-inflammatory drugs
SR	Slow release / modified release drugs
OA	Osteoarthritis
OR	Odds ratio
OTC	Over the counter drugs
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
S.D.	Standard deviation
SF-36	Short Form 36 questionnaire
SPSS	Statistical package for the social sciences
TKR	Total knee replacement
TM	Trademark
THSD	Tukey's honestly significant difference
WOMAC	Western Ontario MacMasters Universities Osteoarthritis Index

Declaration

This is to certify that work submitted in this thesis is the result of original research. It has been conducted substantially by myself with assistance as outlined below. It has not already been accepted for any degree and publications arising from the thesis are appended. All authors and works to which reference has been made are fully acknowledged.

Work contained in this thesis reflects work conducted as part of a large project funded by the Department of Health. As such, a multi-disciplinary steering committee comprising of Prof. Michael Doherty, Dr Adrian Jones, Dr Kenneth Muir, Dr Sheila O'Reilly and Dr Joan Bassey, monitored the design and conduct of the trial. Data collection, treatment provision and general administration of the trial were conducted by myself, and four other research assistants (Louise Naylor, Anna Follows, Elizabeth Williams and Maureen Smith). Alex Sutton, Ben Palmer and Sarah Smith provided statistical advice on the project. Some data relating to medical costs for the final 12-month period were collected as part of a separately funded project by the Department of Health. This data collection was performed by Paddy Hawtin, Amanda Butler, and Gail Faulkner.

Signed: _____

Date: 28/7/01

Acknowledgements

I would like to take this opportunity to thank the people who have helped to bring this study to fruition. Firstly, I would like to thank my tutors – Prof. Michael Doherty and Mr Paul Miller, for their support and encouragement. Their assistance has been invaluable. I would also like to thank all members of the Community Osteoarthritis Research Group, who dedicated their time and expertise, and to all those employed on the study to assist with data collection.

Technical support was provided by the Nottingham City Hospital Medical Physics department, and I would particularly like to thank Matt Dunn and Keith Rickers for their patience and technical expertise. Sarah Pacey, Senior Pharmacist at Nottingham City Hospital, organised the supplies of dolomite tablets, and Cliniband and Dynaband provided the exercise bands used throughout the study.

I would also like to thank the doctors and other support staff at the participating surgeries for their time and facilities. In addition, the commitment of the volunteers who participated in the trial made the whole study possible.

On a more personal note I would like to thank my friends and family for their encouragement and patience - particularly my husband Gary and my parents, without whom this thesis would not have been possible. I would also like to acknowledge the part played by Alex Sutton and Nicola Cooper, who provided statistical advice and friendship at times when it was needed most.

To my parents for their love and support throughout

my years of education.

Summary

This thesis describes a set of inter-related studies that address the medical management of knee pain in the community. It is presented as a health services research project and is multidisciplinary in nature (including epidemiology, research methodology, clinical issues, economic evaluation and medical statistics). A community-based sample has been chosen as being most appropriate for study since the majority of patients receive their treatment within primary care. A pragmatic approach has been adopted in order to achieve broadly generalisable results.

In chapter one, an introduction to the relevant issues and current debates surrounding the management of osteoarthritis and knee pain are outlined. Literature was searched from relevant electronic databases including MEDLINE, the Cochrane Database of Systematic Reviews, DARE (Database of Reviews of Effectiveness), the NHS Economic Evaluation database and the HTA web site. Further references were obtained by hand searching retrieved articles. Whilst this was not intended to be an exhaustive systematic review of the literature, published reviews by other authors were identified in the literature wherever possible. No specific timeframe was adopted for the search. Nevertheless, more recent studies tended to be better executed and designed in the light of existing knowledge. As a result, emphasis has been placed on these findings. The advantage of such an approach over a full systematic review is that it is able to provide a broad introduction to the field within the time and word limits available to the thesis. Clearly, further interrogation of additional

databases, using more structured search terms, would undoubtedly reveal further relevant literature.

Chapter two describes the intervention study and includes results of the initial postal survey and the subsequent randomised controlled trial (RCT). For the RCT a factorial design has been employed in which exercise therapy is compared with telephone support, a placebo health food product and a no intervention control group. The primary outcome is self-reported knee pain at 24 months and has been assessed using a knee-specific instrument (WOMAC). Other secondary outcomes include knee specific stiffness and physical function, quadriceps muscle strength, anxiety and depression (HADs) and more general indicators of quality-of-life (SF-36 physical function and EuroQol EQ-5D). Regression analysis has been used in order to identify possible predictors of response that may be useful in directing future research activity.

Chapter three presents cost-of-illness data relating to the treatment of knee pain. It describes patient-specific cost data collected for volunteers during the 6-month period prior to participation in the RCT. Whilst a societal perspective has been adopted, the primary focus is on costs to the health provider and to the patient. Total costs have been collected in addition to knee-specific costs since patients with osteoarthritis are reported to incur higher costs than their non-arthritic controls for a range of medical conditions. Regression analysis has been used in order to identify factors associated with high primary care costs.

Finally, chapter 4 describes the economic evaluation of the study interventions. This included cost-effectiveness and cost-utility analyses.

1 Introduction

1.1 Osteoarthritis

1.1.1 What is osteoarthritis?

Osteoarthritis (OA) is a chronic locomotor condition, most commonly associated with the elderly. Pathologically it involves the loss of articular cartilage in synovial joints and changes in the underlying bone at joint margins (Doherty et al. 1997). Clinically, OA may result in joint pain and tenderness, limited range of movement, crepitus, mild effusion and deformity. Most commonly affected sites include the knees, hips, hands and spine (Lawrence et al. 1966). It is associated with considerable morbidity, particularly in relation to locomotor difficulties and limitations in activities of daily living (Davis et al. 1991).

OA is not a recent condition, nor is it confined solely to man. Evidence of osteoarthritic changes in the fossilised remains of a variety of animals, prehistoric man and even dinosaurs, points to its extensive history (Jurmain and Kilgore, 1995; Rogers et al. 1981).

Traditional views of the pathogenesis of OA have relied on the concept of mechanical 'wear and tear'; OA being seen as the inevitable result of ageing. However, more recent evidence suggests a far more active process of regeneration and metabolic change. It is now believed that the features commonly observed in an OA joint reflect the normal repair process (Hutton,

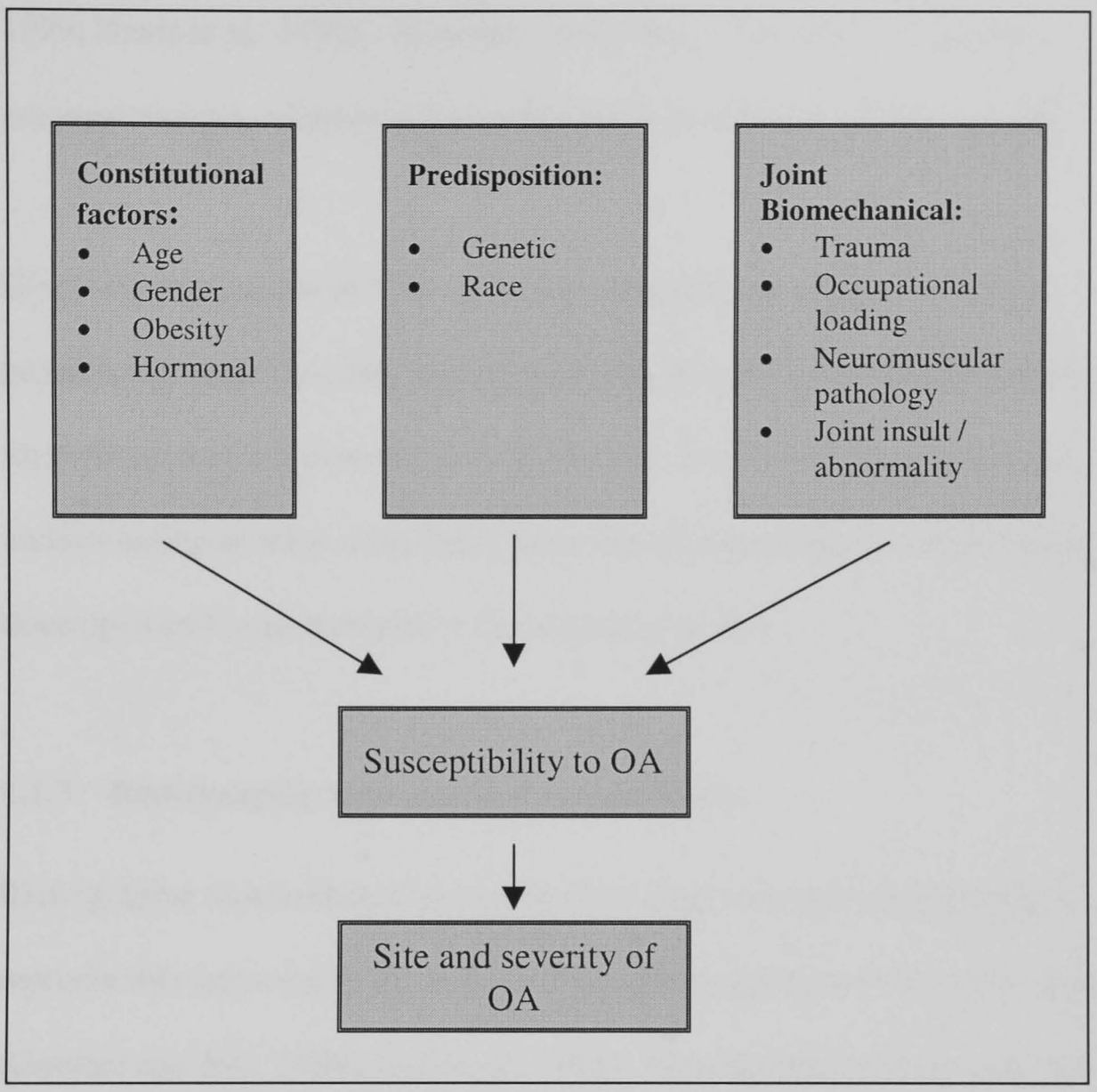
1989). It is only when a discrepancy arises between the demands placed on a joint and the regenerative capacity of that joint, that failure (i.e. symptomatic OA) results (Doherty et al. 1997).

The belief that OA represents an essentially reparative process has caused renewed interest in its study. A better understanding of the development of symptoms, and potential treatment options for the prevention of disability are key issues for future study.

1.1.2 Aetiology of osteoarthritis

Current models for the aetiology of OA involve the complex interplay of predisposing factors, constitutional (systemic) and local biomechanical factors (Figure 1).

Figure 1 Current model of the aetiopathogenesis of OA (adapted from Dieppe and Kirwan, 1994)



OA is no longer thought of as a single disease, but rather as a heterogeneous group of conditions affecting different joint sites. This belief has been strengthened by recent evidence suggesting that the aetiology of OA may vary according to the site of involvement (Cooper et al. 1994).

It is now understood that different risk factors may account for the incidence of disease at different sites. For example, obesity has consistently been identified as a powerful risk factor for the development of knee OA (Sandmark et al.

1999; Hart et al. 1999; Hart and Spector, 1993; Davis et al. 1990), but findings have been more inconsistent in relation to hip OA (Oliveria et al. 1999; Davis et al. 1990). Similarly, prevalence of knee OA is greatest amongst women, whereas this is not the case for hip OA (Felson, 1988).

Given the importance of 'site' in determining the aetiology of OA, it is possibly not surprising that past research has produced conflicting results in the identification of possible risk factors for OA. It is only through a greater understanding of these underlying processes that appropriate measures can be developed and implemented for the treatment of OA.

1.1.3 Radiographic assessment of osteoarthritis

Radiographic assessment of osteoarthritic change is relatively inexpensive, reproducible and reflects the major pathophysiological features of the disease (Gunther and Sun, 1999; Jacobsson, 1996). Nevertheless, radiographs lack sensitivity in a number of situations. They are particularly insensitive in the detection of early OA changes, and are limited in their ability to detect disease progression. Recent technological advances such as the use of ultrasound, or magnetic resonance imaging, may ultimately provide more useful insights into the disease process (Boegard et al. 1998; Buckland-Wright, 1997). Nevertheless, X-rays currently play an important role in establishing the presence of OA for both clinical and epidemiological study.

It was not until the 1950s that Kellgren and Lawrence developed the first formal classification system for OA (Kellgren and Lawrence, 1957). (Table 1). This early grading scheme has been the "gold standard" for many years and was adopted as the standard criteria for epidemiological research by the World Health Organisation in 1961. A grade of 2 or above is now generally accepted as the minimum requirement for the case definition of OA, and many of the population surveys conducted to date have relied on this system (McAlindon et al. 1993a; Felson et al. 1987).

Table 1 Kellgren and Lawrence grading scheme for osteoarthritis.

Grade	Radiographic Criteria
0	Normal
1	Doubtful narrowing of joint space, possible osteophyte.
2	Definite osteophyte, absent or questionable narrowing of joint space
3	Moderate osteophyte, definite narrowing, sclerosis, possible deformity.
4	Large osteophyte, marked narrowing, severe sclerosis, definite deformity.

Nevertheless, the Kellgren and Lawrence grading scheme has been criticised in recent years. Confusion as to the exact wording of the criteria has led to studies of relatively poor comparability; even when the standard criteria were claimed to have been used (Spector et al. 1991). In addition, the exclusion of grade 1 (mild OA) by the majority of researchers means that early OA changes are often ignored. Finally, the over-reliance on osteophyte formation as a

defining feature of OA has been questioned (McAlindon and Dieppe, 1989; Wood, 1976).

Many researchers now prefer the grading of individual features (osteophyte, joint-space narrowing, sclerosis, alignment and bone attrition) within specific joints or compartments (McAlindon et al. 1993b; Cooper et al. 1992; Menkes, 1991). This has led to the development of several new grading atlases (Burnett et al. 1994; Altman et al. 1986b). Further development and validation of these atlases in a variety of clinical and epidemiological settings is now needed (Jacobsson, 1996).

1.1.4 Prevalence of osteoarthritis

OA is a condition of slow and insidious onset. As such, it has traditionally been examined through cross-sectional surveys of prevalence, rather than by incidence of disease (Croft, 1990). In addition to the early work by Kellgren and Lawrence, several large-scale studies have been conducted over the last 20 years, the main features of which are summarised in Table 2.

These studies provide the basis for our growing understanding of the course and development of OA. Nevertheless, different studies have produced very different estimates of prevalence. Given the variability in different epidemiological and radiographic techniques, this is possibly not surprising

(Spector and Hochberg, 1994). However, certain aspects of the disease consistently emerge.

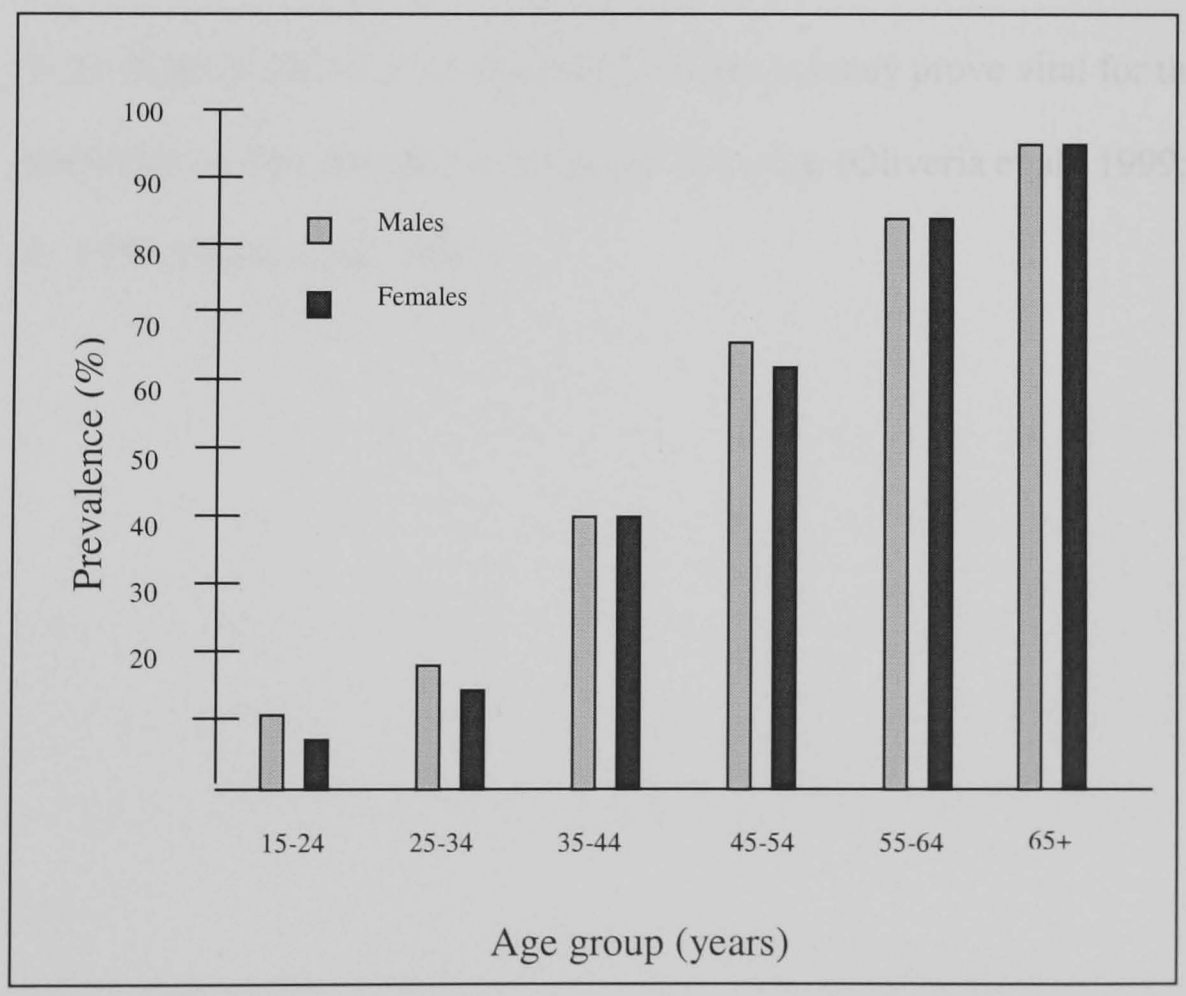
OA is by far the most prevalent chronic joint condition (Lawrence et al. 1989). Estimates suggest that OA is present in 8.7 to 12.3% of the population (Rothfuss et al. 1997). Prevalence varies greatly between joints (van Sasse et al. 1989). The most commonly affected joints are the hands, knees, hips and apophyseal joints of the cervical and lumbar spine (Bagge et al. 1991; Lawrence et al. 1966).

Table 2 Summary of recent prevalence studies for knee OA.

Study	Reported by	Subjects	Study type	X-rays	X-ray grading scheme	Prevalence of knee OA
NHANES-1 1971-1975 *National Health & Nutrition Examination Survey*	Davis et al. (1992)	4056 US adults aged 45-74 yrs	National probability sample. Prospective cohort study	Anteroposterior non-weight bearing OA = grades 1-4	Kellgren & Lawrence	Men (5%) Women (10%) 41% of these symptomatic
NHEFS 1980-1982 *National Health & Nutrition Examination Survey Epidemiological Follow-up*	Davis et al. (1991)	2989 adults from previous NHANES-1 survey	Prospective cohort study	None	N/A	Men (5%) Women (9.5%)
Framingham Osteoarthritis Study 1983-1985 1992-1993	Felson et al. (1987) Felson et al. (1997)	1805 adults aged 63-94 years Unclear 598 X-ray negative subjects from 1983-85 cohort were X-rayed	Part of Framingham Heart Study Cohort. Prospective cohort study	Anteroposterior weight bearing. OA = grades 2-4 As above	Kellgren & Lawrence + features As above	36% X-ray 9% X-ray + symptoms 15.6% incident disease since earlier X-ray
Johnston County Osteoarthritis Project	Jordan et al. (1997)	1192 African-American & Caucasian adults aged >45 yrs from rural N. Carolina	Probability sample. Prospective cohort study.	Antero-posterior weight bearing. OA = grades 2-4.	Kellgren & Lawrence	19% all subjects
Zoetermeer Study	van Sasse et al. (1989)	6585 inhabitants aged >20 yrs of a Dutch village	Random population sample. Cross-sectional survey	Type not specified. OA = grades 2-4.	Kellgren & Lawrence	18% all subjects
Baltimore Longitudinal Study of Aging 1984-1989	Lethbridge-Cejku et al. (1995)	675 Caucasian adults aged 19-92 years	Cross-sectional survey	Antero-posterior weight bearing OA = grades 2-4	Kellgren & Lawrence + individual features.	Men (11%) Women (10%)
Goteborg Study 1971-1972 1976-1977	Bagge et al. (1992)	266 adults aged >70 years	Cross-sectional & prospective (followed-up for ten years)	Antero-posterior weight bearing with slight flexion OA = grades 2-4.	Kellgren & Lawrence	Men (51%) Women (56%)
Chingford Study 1988-1989 1993	Hart and Spector, (1993) Hart et al. (1999)	1003 women aged 45–64 years 830 (83% of original population)	Cross-sectional survey Prospective cohort study	Antero-posterior weight bearing OA = grades 2-4 As above	Kellgren & Lawrence	12% X-ray 6% X-ray + symptoms Incidence 3%/year

The importance of age in determining the presence of OA has been consistently identified (Davis et al. 1992; Felson et al. 1987; Lawrence et al. 1966). Lawrence et al. found that almost everyone over the age of 65 years had at least one joint with arthritic changes of grade 2 or greater. As is graphically demonstrated in Figure 2, prevalence increases steadily with age. However, prevalence may plateau in later life (Bagge et al. 1992).

Figure 2 Graph showing the prevalence of OA (grades 2-4) by age (from Croft, 1990). Data from Lawrence et al. (1966); Kellgren & Lawrence (1958).



Somewhat contradictory findings have been found with regard to gender differences in the prevalence of OA. Nevertheless, rates are generally reported to be higher for women than they are for men (Felson et al. 1987), especially for the hand and knee joints, and in the older age groups (van Sasse et al. 1989).

Much is still to be achieved in the development of accurate prevalence figures. In particular, clarity in the definition of clinically relevant cases will help to elucidate the true burden of disease (Petersson, 1996). In addition, the recent trend towards increasing numbers of prospective incidence studies is clarifying the findings of earlier cross-sectional studies and may prove vital for the elucidation of risk factors for disease progression (Oliveria et al. 1999; Hart et al. 1999; Felson et al. 1997).

1.2 Knee Osteoarthritis

1.2.1 Defining knee osteoarthritis

Recognition of the importance of site-specific definitions of OA has led to renewed efforts to develop clear and reliable case criteria for epidemiological investigation of the knee (Hart and Spector, 1995). Future developments may expand our current understanding of the factors relevant to sensitive and specific diagnosis. In particular, the development of "biological markers" of disease shows promise (Clark et al. 1999; Lohmander and Felson, 1997). Nevertheless, for the purposes of this study, the two most commonly held definitions of OA (radiographic assessment and clinical assessment) are most relevant.

1.2.1.1 Radiographic definitions of knee osteoarthritis

Epidemiological studies have traditionally favoured the use of radiographic evidence of structural abnormality in establishing case status. As yet, consensus in producing an appropriate and consistent classification has proved surprisingly difficult. Indeed, until 10 years ago, specific criteria for admission to clinical trials were only reported in 20% of published studies (Altman, 1995).

It is now recognised that no one grading system is suitable for the study of OA at all sites (Murphy, 1995). This has led to the development of atlases specific to individual joints, including the knee (Altman et al. 1995; Burnett et al.

1994). The importance of the patellofemoral joint as an independent factor in the development of knee pain has led to recommendations for the inclusion of skyline radiographs, which are more sensitive in detecting abnormality and change with time (Lanyon et al. 1996; Jones et al. 1993).

Possibly the greatest debate surrounding the grading of radiographs is in the dominance of individual features. The Kellgren and Lawrence scheme heavily emphasised the importance of osteophyte formation. It has since been argued that osteophytes can represent a normal feature of ageing (Wood, 1976), and that the importance of joint space narrowing should not be ignored. More recent findings suggest that both aspects may be important in determining different aspects of the disease. In particular, the presence of osteophytes (especially in the patellofemoral joint) may better predict pain reporting (Cicuttini et al. 1996), but joint space narrowing may be a better indicator of disease severity and progression (Altman et al. 1987).

Regardless of the criteria used, discordance between radiographic evidence of disease activity and self-reported pain occurs consistently (Creamer and Hochberg, 1997). Patients with severe radiological change are more likely to report pain than those with mild arthritic change. Nevertheless, the relationship between the two is not strong. The pioneering work by Kellgren and Lawrence was the first to identify the possible discordance between radiographic evidence of disease activity and self-reported symptoms (Lawrence et al. 1966). Their population-based surveys of the 1960s revealed considerable

levels of discordance (20-80%); actual rates being dependent upon the site of involvement.

The continued disparity between symptom reporting and radiographic evidence of disease (Davis et al. 1992; Felson et al. 1987) has caused concern about the over-reliance on radiographic evidence alone. The American College of Rheumatology (ACR) has issued recommendations based on a combination of both radiographic and clinical criteria and has emphasised the importance of "clinically relevant" cases (Altman et al. 1986a).

1.2.1.2 Clinical definitions of knee osteoarthritis

In 1986, a subgroup of the American College of Rheumatology was convened in order to establish a reliable set of clinical criteria for the classification of OA (Altman et al. 1986a). This work was based on consensus agreement as to the most important features of OA. The discriminative ability of these features was then assessed in a group of 257 hospital referred OA patients compared with a control group (of which 55 had rheumatoid arthritis and 52 had a variety of other musculoskeletal complaints). The combination of findings with the highest levels of specificity and sensitivity are shown in Figure 3.

Figure 3 Summary of the ACR criteria for the clinical classification of knee OA (Altman, 1991).

1	Knee pain for most days of prior month.
2	Crepitus on active joint motion.
3	Morning stiffness of the knee ≤ 30 minutes.
4	Age ≥ 38 years.
5	Bony enlargement of the knee with crepitus.
6	Bony enlargement of the knee without crepitus.

Osteoarthritis is adjudged to be present if any one of the following three sets of criteria is fulfilled: 1, 2, 3 and 4.
1, 2, 3 and 5.
1 and 6.

These criteria depend on the presence of "knee pain" for a definition of OA, and are therefore a measure of symptomatic OA. Such a definition is probably most appropriate for epidemiological study, since it is symptomatic patients who represent the greatest burden to society. Nevertheless, certain limitations have been identified. Firstly, it is no easy matter to identify presence of pain. The reporting of pain is known to be highly variable (Bellamy et al. 1990) and to be multifaceted (Creamer et al. 1999). In addition, the wording of pain questions can influence reported prevalence (O'Reilly et al. 1996; Spector et al. 1991). It may even be possible that different questions are better associated

with different aspects of the disease; some being more able to identify radiographic changes (Cicuttini et al. 1996) and others disability and pain (O'Reilly et al. 1996). Various questions have been used in recent years (Table 3), although consensus as to the most appropriate has yet to be reached.

Table 3 Summary of the pain questions used in epidemiological studies.

Pain question:	Used by:	Comments:
Have you ever had pain in or around the knee on most days for at least a month? *If so, have you experienced any pain during the last year?*	NHANES-I (Davis et al. 1992) NHEFS (Hochberg et al. 1989) Framingham Study (Felson et al. 1987) Bristol Study (McAlindon et al. 1993a) Baltimore Longitudinal Study of Ageing (Lethbridge-Cejku et al. 1995)	• Both sections of the question must be positive for subjects to be classified as having knee pain. • NHANES-I also classified subjects as having knee pain if they reported pain during range of motion assessment. • The Framingham study only used part 1 of the question. • The Bristol Study scored each knee separately. • The Baltimore Study of Ageing used these questions to give an indication of "pain ever" (part 1 only) and "current pain" (parts 1 & 2).
Have you had pain within the last year in or around the knee that occurred on most days for at least a month?	(O'Reilly et al. 1996)	• This is a modified version of the NHANES-I question. It was used to assess the impact of minor word changes on pain reporting. • Resulted in lower estimates of pain prevalence than the NHANES-I version.
Have you had knee pain on most days of the last month?	ACR criteria for clinical classification	• This question has proved very insensitive in population studies. • It may be most useful in a hospital setting. • Associates with disability better than with pain.

Have you had an episode of knee pain lasting ≥ 15 days in the last month? *Have you had two or more episodes of knee pain in the last year?* *Have you had a past episode of knee pain lasting ≥ 15 days?*	(Cicuttini et al. 1996)	• Patients were asked all three questions. Responses were assessed for their ability to predict radiographic indicators of disease. • Question 2 was most closely associated with osteophyte formation (in all compartments).
Have you had any pain or other complaints about your joints in the last month? *If yes, can you point to the painful joint?*	Rotterdam Study (Hopman-Rock et al. 1996)	• This question was asked 3 times at subsequent assessments (twice in 1991 and once in 1993) • Pain was classified as: Chronic = yes x 3. Episodic = yes x 2. Sporadic = yes x 1.
Do you get knee pain on most days? *If yes, how severe is that pain: mild, moderate or severe?*	Johnston County Osteoarthritis Project (Jordan et al. 1997)	• Indication of severity was based on the worst knee.

A further difficulty with the ACR criteria is that poor reliability and reproducibility limit the assessment of clinical features. Considerable variation has been found in inter-observer reliability for the assessment of clinical features in a hospital population (Jones et al. 1992). In addition, examination of levels of agreement between the three possible ACR sets of criteria has led to varying estimates of prevalence (Schouten and Valkenburg, 1995) Possibly the most fundamental problem for the use of the ACR criteria for epidemiological study is that they were developed and tested in a hospital setting. The ability to generalise to a community-based sample is as yet

unknown (Schouten and Valkenburg, 1995), and the use of controls with rheumatoid arthritis (RA) meant that these patients were likely to have some degree of joint space narrowing themselves (McAlindon and Dieppe, 1989). This may explain the poor discriminative ability of joint space narrowing for these criteria.

Despite these limitations, the ACR criteria represent the first structured attempt to accurately define the clinical symptoms of OA. Further work is now required to assess the validity and reliability of such measures in a variety of both clinical and community settings (Jacobsson, 1996).

1.2.2 Aetiology of knee osteoarthritis

The largest body of evidence to examine the putative risk factors for knee OA comes from NHANES-I, its subsequent follow-up (NHEFS) and the Framingham and Chingford studies. Evidence from the Framingham and Chingford studies is particularly informative since it allows risk factors to be examined prior to disease onset (Hart et al. 1999; Felson et al. 1997)

A summary of the most commonly identified risk factors for radiographic knee OA is presented (Table 4).

Table 4 Risk factors for radiographic knee OA (adapted from Felson, 1990).

Associated with knee OA	• Increasing age • Female gender • Obesity • Muscle dysfunction • Knee trauma / injury • Occupational knee bending / physical labour
Association not clear	• Oestrogen use (may be protective in women) • Chondrocalcinosis • Sport and exercise
Negative association	• Smoking

Prospective data from the Framingham Study allowed an examination of risk factors for new cases of radiographic knee OA in elderly subjects (McAlindon et al. 1999; Felson et al. 1997). This study examined radiographs taken at baseline (1983-85) and compared them with radiographs taken again in 1992-93. New cases of knee OA were identified (93 of 598 patients without knee OA in the initial survey), and baseline risk factors were assessed in relation to subsequent development of OA. The study confirmed many of the earlier cross-sectional findings. In addition, it was able to clarify the role of certain factors. The presence of chondrocalcinosis at baseline for example, had little effect on future development of knee OA. Perhaps more surprisingly, the study pointed to considerable increased risk of knee OA in habitually active elderly subjects. An adjusted odds ratio (OR) of 3.3 was observed for patients in the highest quartile of physical activity at baseline compared with those in the lowest quartile. This finding demonstrated a dose response effect, with higher risk being found with each increase in physical activity. The exact nature of

the observed relationship is as yet unclear, although a markedly increased risk was observed for obese individuals. Previous studies have pointed to the possibility of increased risk for runners and elite athletes (Spector et al. 1996). Nevertheless, the levels of activity being reported by this elderly population were more comparable with normal activity levels observed in younger subjects (high physical activity was defined as heavy housework or intensive exercise).

The importance of obesity in the development of knee OA was confirmed in the Chingford study (Hart et al. 1999). These investigators examined possible risk factors for 715 individuals who developed radiographic evidence of disease activity after a 4-year period of follow-up. Those with incident knee OA were heavier, older, had more hand OA and reported more knee symptoms at baseline. In contrast to the Framingham study, high physical activity showed no association with disease incidence, although findings were limited by lack of power in relation to highly active individuals.

Work to date has concentrated on risk factors for the development of OA in the tibiofemoral joint. However, different risk factors may be responsible for OA within different compartments of the knee. Cooper et al. compared subjects with symptomatic OA (tibiofemoral and /or patellofemoral OA) with age and sex matched controls (Cooper et al. 1994). Despite relatively small numbers (obesity was observed in only 13 cases with tibiofemoral OA, and 10 with patellofemoral OA), some interesting observations were possible. In particular,

obesity and meniscectomy were associated with tibiofemoral OA, whereas patellofemoral OA was associated with a family history of knee OA and the presence of Heberden's nodes. The lack of association between obesity and patellofemoral OA has also been found in a hospital-based population (Ledingham et al. 1993). Indeed, even palaeopathological evidence has been used to suggest that tibiofemoral OA is a relatively 'new' disease, and that this may support its association with obesity and menisectomy (Rogers and Dieppe, 1994).

Future work into the putative risk factors for OA should recognise the importance of these findings, and should make greater effort to identify the specific site of involvement.

1.2.3 Prevalence of knee osteoarthritis

The knee is one of the most commonly affected joints (van Sasse et al. 1989; Lawrence et al. 1966). Exact prevalence rates vary, but radiographic tibiofemoral OA is generally reported to be present in 3.8% of those aged 25-74 years, and between 14% and 30% for persons over the age of 45 years (Petersson, 1996).

As with OA in general, knee OA is strongly associated with age. By the age of 75 years, prevalence has been found to be as high as 40 - 60% (Bagge et al. 1992). Gender is more strongly associated with knee OA than it is at other

joint sites. Women are generally reported as having a higher incidence of knee OA than men (Croft, 1990). Nevertheless, a reversal of this pattern is found for people aged under 45 years. This finding may reflect different aetiological processes, with men being more likely to develop early OA as a result of knee injury or excessive joint loading (Cooper, 1995).

1.2.4 Prevalence of symptomatic osteoarthritis

Few studies have examined the prevalence of pain as an independent issue. Considerable variation exists in the available data and is particularly governed by the wording of pain questions. For example, the Baltimore Longitudinal Study of Ageing reported knee pain prevalence of 23% for "ever having pain" and 15% for "pain within the last year" (Lethbridge-Cejku et al. 1995). Using the ACR criteria of "pain present for most days of the previous month", rates have been reported as low as 2.3% (Spector et al. 1991). Nevertheless, most studies report knee pain prevalence in subjects over 45 years as being between 12 and 38% (Spector and Hart, 1992).

The discordance between radiographic evidence of OA and symptom reporting has already been highlighted. Lawrence et al. (1966) suggested that only 51% of people with knee OA of grade 2 or more (aged over 45 years) reported knee pain. Conversely, of those with no or only mild OA (grade 1 or less), 33% reported pain. Analysis of the NHANES data (Davis et al. 1992) revealed similar findings with symptomatic OA in 41% of those with knee OA of grade

2 or more (for ages 45-74), and symptoms in 29% of people with no or only mild OA.

More recent studies have revealed an even weaker association between radiographic status and pain reporting. The Framingham (Felson et al. 1987) and Zoetermeer (Claessans et al. 1990) studies suggest that pain may be present in only 29% (Framingham, aged 63-94) to 24% (Zoetermeer, aged 20-80+) of subjects with a minimum of grade 2 OA. Variation between the studies can possibly be explained by differences in methodology. The work by Lawrence et al. and the NHANES data are based on non-weight bearing radiographs. This would have the effect of underestimating the severity of OA, and would result in subsequent misclassification. In addition, different criteria for "pain" were used by the different studies. NHANES-I, for example, used either self-reported knee pain or pain during formal examination as their criteria for symptomatic knee OA (Davis et al. 1992). This would inevitably result in higher levels of pain reporting than by questionnaire assessment alone.

Possible reasons for the poor association between physical change and symptom reporting are not entirely clear (Sharma and Felson, 1998). Discordance may simply be a result of the relative insensitivity of X-ray imaging (in which case, use of more recent imaging techniques may reveal a stronger association). The inclusion of the patellofemoral joint in future studies may also result in stronger agreement. It has been suggested that up to 24% of females who report knee pain have got isolated patellofemoral OA (Creamer

and Hochberg, 1997). Despite such allowances, it is unlikely that discordance will disappear completely. Consequently, it is possible that knee pain and radiographic evidence of knee OA represent different entities, and that each has different putative risk factors.

1.3 Knee pain and osteoarthritis

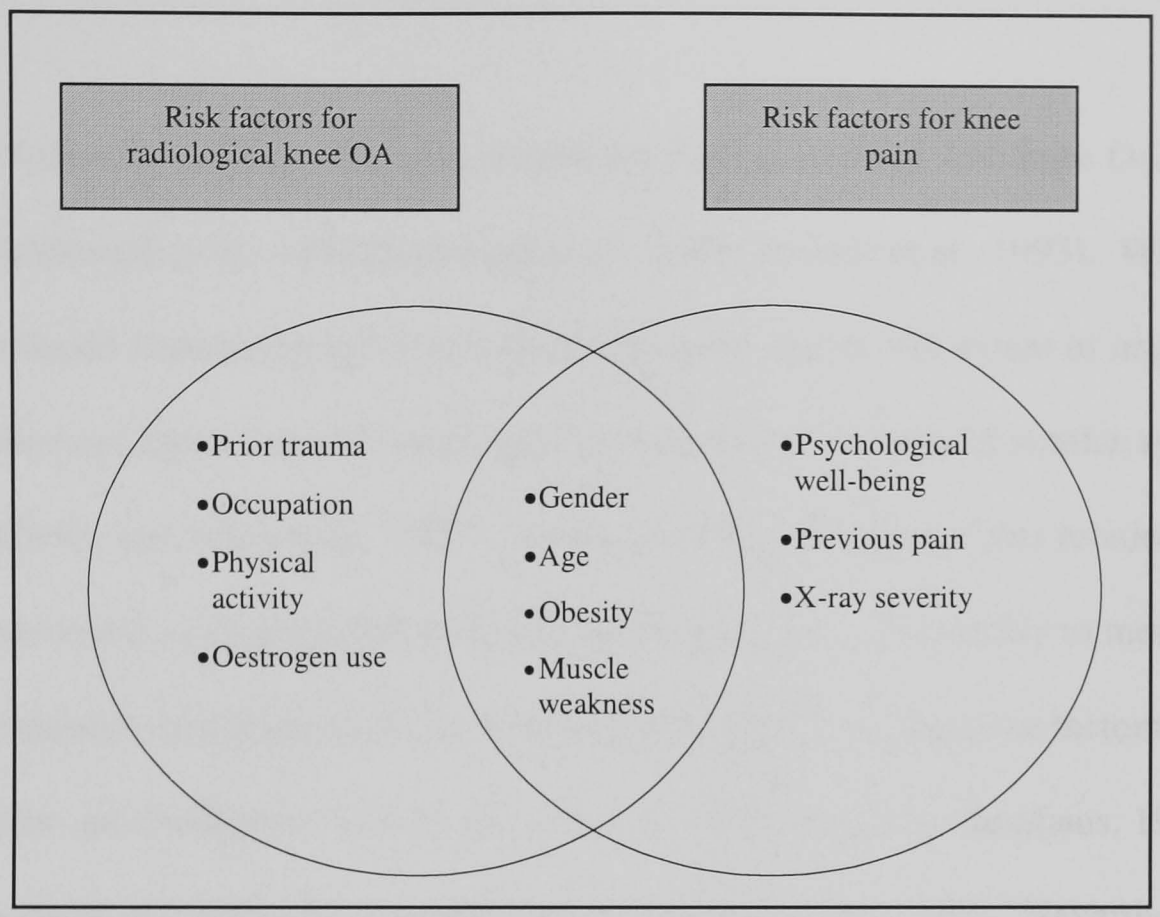
1.3.1 The importance of knee pain

The role of knee pain as an entity for epidemiological study has only recently gained credence (Laupacis et al. 1992; Hadler, 1992). The shift away from radiographic change as the primary indicator of disease activity is significant, for it is symptomatic patients who represent the greatest burden to society. In addition, greater understanding of the psychosocial aspects of symptomatic OA has resulted in renewed interest in alternative treatment strategies, such as patient education or social support (Hadler, 1992).

1.3.2 Aetiology of knee pain

Current understanding of the aetiology of knee OA has already been outlined. Greater understanding of the aetiology of knee pain reveals a slightly different pattern of association. Once again, the Framingham and NHANES studies have proved informative (Felson, 1990; Hochberg et al. 1989). A summary of our current understanding of the possible interaction of risk factors is presented (Figure 4).

Figure 4 Summary of the interaction of risk factors associated with radiographic knee OA and knee pain



Of the factors outlined in Figure 4, low muscle strength and poor psychological well-being are of particular relevance to the current study. Both have been identified as risk factors for the development of symptomatic OA and merit further discussion.

1.3.2.1 Muscle weakness

The knee joint is a complicated structure. Its stability depends on the cruciate and collateral ligaments, the synovial capsule and the muscles crossing the joint. The bone morphology of the knee constitutes little to its overall stability. As a result, the knee is particularly vulnerable to subluxation and damage. Any

impairment in muscle strength not only reduces joint stability, but also reduces the limb's ability to absorb shock during ambulation.

Weakness in the quadriceps muscles has been associated with knee OA (Slemenda et al. 1998; Slemenda et al. 1997; Dekker et al. 1993). Whilst reduced muscle strength is a normal feature of ageing, the extent of impairment seen in people with OA seems greater than that of controls of similar age (Fisher and Pendergast, 1997). However, the importance of this relationship is inevitably confounded by methodological problems. The ability to measure voluntary muscle contraction is largely dependent on subjective factors such as pain, psychological distress and voluntary effort (Ikai and Steinhaus, 1961). As a result, it is difficult to quantify the true nature of the deficit. Nevertheless, recent work involving the use of electrical stimulation of the muscle during muscle testing (twitch superimposition), has proved useful in supporting the presence of reduced quadriceps activation in subjects with knee pain (O'Reilly et al. 1998).

The possible causes of such muscle impairment are far from clear. The simplest interpretation is that muscle strength is lost due to reduced activity and loading of the painful joint. However, whilst disuse appears to plays a role in the development of muscle weakness, it is not sufficient to explain the extent of impairment observed (Brandt, 1997). A recent community-based study examined 462 volunteers aged 65 and over (Slemenda et al. 1997). Subjects were divided into four groups according to presence or absence of radiographic

OA, and presence or absence of knee pain. This study suggested that muscle weakness was greatest in people with radiographic OA, regardless of pain status. Loss of muscle function was thus observed in the absence of joint pain for some people, and would therefore suggest that disuse is not the primary cause of muscle weakness.

An alternative argument is that the observed reduction in quadriceps strength in knee OA is due, at least in part, to arthrogenic muscle inhibition. Arthrogenic inhibition is not a new concept (Harding, 1929) and involves the inhibition (or reduced activation) of muscle due to abnormal processes in the joint itself (Young, 1993). Alternatively it may prove to be other aspects of the diseased joint, such as joint laxity, which prove to be more important in the aetiology of knee OA (Sharma et al. 1999).

1.3.2.2 Psychological well-being

The importance of psychological variables as predictors of pain and disability in knee OA was first highlighted by Summers et al. (1988). This small, hospital-based study identified depression, anxiety and coping style as being important independent risk factors for the reporting of pain and functional impairment in both knee and hip OA. Subsequently, several studies have examined the impact of psychological variables (Manninen et al. 1997; Davis et al. 1992; Salaffi et al. 1991). Some of the factors thought to be associated with the presentation of knee pain are outlined in Table 5.

Table 5 Psychological factors associated with knee pain and disability.

Cognitive-behavioural factors:	**Health impact:**
Anxiety and depression	• Increased anxiety and depression are associated with increased pain and disability. (Manninen et al. 1997; Summers et al. 1988) • Also associated with increased health care costs (Andersson et al. 1999) • Mental distress (including depression, nervousness, loneliness and sleep disorders) is associated with an increased risk of hip fracture (Forsen et al. 1999)
Coping strategies *(the ability of a person to adapt to a challenge or to successfully confront a stressor)*	• Strategies associated with improved psychological well-being and greater self-efficacy include: information seeking, problem solving and cognitive restructuring (thinking about people worse-off than self) • Strategies associated with worse psychological well-being, reduced self-efficacy, and increased pain, depression and helplessness include: wishful thinking, self-blame and activity avoidance. (Blalock et al. 1995; Manne and Zautra, 1992)
Self-efficacy *(the belief that one can perform a specific behaviour or task in the future)*	• High self-efficacy is related to better functional capacity and health status (Lorig et al. 1985) • May be the critical element in successful education programmes (Lorig et al. 1989a) • May be a mediating factor in successful exercise therapy (Rejeski et al. 1998)
Personality type	• Introverts may have a lower pain threshold than extroverts (Bird and Dixon, 1987) • Hypochondriacs are more likely to report pain (Lichtenberg et al. 1998)
Locus of control *(the belief that outcomes are under the control of either one's own behaviour [internal locus of control] or by factors such as chance or other people [external locus of control]*	• An external locus of control is associated with increased depression, and distress associated with pain (Skevington, 1983)
Learned helplessness *(the degree of inertia and inactivity observed when people experience uncontrollable stressors)*	• Associated with pain and disability (Creamer et al. 1999; Nicassio et al. 1985) • Also linked with depression (Stein et al. 1988)

Table 5 (continued).

Environmental factors:	**Health impact:**
Social support	• High social support is generally associated with improved function (Wallston et al. 1983)
Social participation	• Low social participation has been associated with increased mortality (Steffen et al. 1998)
Stressful life events *(taxing environmental events)*	• These may include work-related stressors (e.g. job insecurity), or social and family pressures (e.g. illness or marital difficulties) • Associated with increased pain and disability

Understanding the impact of psychosocial factors is limited by methodological difficulties. Most notably, the predominance of cross-sectional surveys means that causal relationships cannot be established. This is particularly important in seeking to understand the relationship between pain, anxiety and depression. Nevertheless, a few prospective studies have suggested that depression may be an important risk factor for the development of future musculoskeletal pain (Croft et al. 1995; Magni et al. 1994) and disability (Manninen et al. 1997). Further work is now needed in order to establish the exact nature of this relationship. Certainly, an association has been observed between depression and the extent to which individuals access medical facilities (Dexter and Brandt, 1994; Katz and Yelin, 1993). Greater understanding of the impact of psychological variables may be especially pertinent for patients seeking medical assistance.

A more fundamental problem in elucidating the role of psychological factors is the difficulty of quantifying psychological processes. Many outcome instruments have been developed for a range of psychosocial variables

including: anxiety and depression, coping strategies, learned helplessness, self-efficacy, locus of control, social support and social participation (Boston et al. 1990; Lorig et al. 1989b; Regan et al. 1988; Brown and Nicassio, 1987; Nicassio et al. 1985; Radloff, 1977; Holmes and Rahe, 1967). The variety and complexity of these instruments often prohibits meaningful comparison and has resulted in potentially conflicting results (Blalock et al. 1995).

For example, in comparing two scales designed to address the use of different coping strategies, the importance of specific questions is apparent. The Pain Management Inventory (Brown and Nicassio, 1987) identifies "active coping" as an appropriate coping strategy, whereas the Coping Strategies Inventory (Tobin et al. 1989) identifies "problem avoidance" as a maladaptive coping strategy. Intuitively, such classification appears logical and informative. However, closer examination of specific questions reveals surprising similarities between the two sub-scales (Table 6).

Table 6 Summary of questions relating to coping strategies as assessed by the Pain Management Inventory and the Coping Strategies Inventory. (Adapted from Blalock et al., 1995).

Active coping strategies (associated with positive outcomes).	**Problem avoidance strategies** (associated with negative outcomes).
"ignoring the pain"	*"I go along as if nothing is happening"*
"distracting attention from the pain"	*"I make light of the situation and refuse to get too serious about it".*

Despite such limitations, recognition of the importance of psychosocial variables in the development of knee pain has resulted in the provision of new and unusual treatment options. In particular, the development of cognitive-behavioural programmes such as the Arthritis Self-Management Programme (Lorig et al. 1999; Lorig et al. 1993b; Lorig et al. 1984) has emphasised the importance of patient education and behaviour modification in the treatment of OA.

1.3.3 Knee pain and disability

The importance of knee pain as an indicator of disability has been identified in several cross-sectional surveys (Jordan et al. 1997; Hofman et al. 1991; Hochberg et al. 1989). Knee pain is particularly associated with lower limb disability; especially in situations involving weight transfer. Walking, rising from sitting, climbing stairs and getting in / out of a car or bed have all been

reported to be increasingly difficult in the presence of knee pain (Odding et al. 1998; Davis et al. 1991). A more unexpected finding is the association between knee pain severity and impairment in upper limb function. The Johnston County OA project (Jordan et al. 1997; Jordan et al. 1996) interviewed 1,272 African-American and Caucasian individuals aged 45 years and over. After adjusting for age, race, sex, BMI and radiographic severity, moderate to severe knee pain was associated with impairment in all 20 of the activities of daily living (from the Health Assessment Questionnaire – HAQ). Indeed, even mild knee pain was associated with 16 of the possible 20 activities. Similar findings were observed in the NHANES-I follow-up study for women with knee OA (Davis et al. 1991).

Several probable reasons for an association between knee pain and upper limb disability have been identified (Jordan et al. 1997). Firstly, the presence of generalised OA would result in greater upper limb involvement than might be predicted from an examination of a single joint. This may explain the stronger effect seen in women since generalised OA is more common in females (Gunther et al. 1998). A further explanation could be the influence of comorbidity, which again is a common feature of people with OA (Gabriel et al. 1999; Hochberg et al. 1995). Finally, the impact of psychological distress should not be ignored. Depression and anxiety have been associated with increased pain reporting (Creamer et al. 1999; Croft et al. 1995), and may well be associated with increased willingness to report disability at multiple sites (Summers et al. 1988).

Recent studies have pointed to several important factors in determining knee related disability. As with knee pain, both muscle strength and psychological variables are important. A cross-sectional study of 200 patients, examined the relationship between radiological, kinesiological and psychological characteristics in patients with hip or knee OA (van Baar et al. 1998a). This study identified significant associations between disability and muscle weakness, range of joint motion and pain coping strategies, but not with radiographic severity. In particular, patients were more disabled if they had weaker muscles (flexion and extension), reduced range of movement, and if they employed coping strategies which involved either resting or worrying. For hip OA (but not knee OA), the presence of pain was also associated with disability.

Similar findings were observed in a community-based study of subjects both with and without knee pain (McAlindon et al. 1993a), although in this study, knee pain was significantly associated with reported disability (along with reduced muscle strength and increased age). Once again, the addition of radiographic status did not improve the model and was assumed to make no independent contribution to disability in these subjects.

1.4 Treatment of knee osteoarthritis

Given the prevalence of OA and its associated morbidity, it is possibly surprising that access to health service provision is not substantially higher than is currently seen (Dieppe et al. 1999). The ability to cope with knee OA is associated with a range of psychosocial factors, but seems to be largely unrelated to disease severity (Salaffi et al. 1991). The need to seek medical assistance for the relief of knee pain may reflect a person's difficulty in coping with the pain and disability of OA, rather than being the inevitable result of the disease itself (Hadler, 1992). Greater understanding of this fact allows flexibility in the investigation of potential treatment options and has led to renewed interest in the benefits of non-pharmacological interventions. In addition, the importance of improving communication between patient and physician (Donovan and Blake, 2000; Britten et al. 2000) and an emphasis on joint decision-making, have gained credence in recent years (Holman and Lorig, 2000; Clark and Gong, 2000).

The current guidelines for the medical management of knee OA, are summarised in Figure 5. Whilst the impact of pharmacological therapies (particularly the use of NSAIDs) for the treatment of OA has been widely explored (Moore et al. 1998; Paakkari, 1994; Dieppe et al. 1993), less is known regarding the use of non-pharmacological therapies. This may be due, at least in part, to the methodological difficulties inherent in the investigation

exercise therapy (Dieppe and Szebenyi, 2000). Other interventions are available for the treatment of knee pain, such as surgery or osteopathy. but these areas fall outside the remit of this thesis. Further discussion of treatment options has therefore been limited to the two areas most relevant to this body of work, namely physical therapy and psychosocial support.

Figure 5 Summary of guidelines for the medical management of knee OA (from ACR subcommittee on OA guidelines, 2000).

Non-pharmacological therapy:

- Patient education (self-management programs)
- Health professional social support via telephone contact
- Weight loss (if overweight)
- Physical therapy:
  - range of motion exercises
  - quadriceps strengthening exercises
  - aerobic exercise programs
  - assistive devices for ambulation
- Knee support
  - patellar taping
  - appropriate footwear
  - lateral-wedge insoles
  - bracing
- Occupational therapy:
  - joint protection and energy conservation
  - assistive devices for activities of daily living

Pharmacological therapy:

- Oral
  - Acetaminophen
  - COX-2-specific inhibitor
  - Nonselective NSAID plus misoprostol or a proton pump inhibitor
  - Nonacetylated salicylate
- Other pure analgesics
  - Tramadol
  - Opioids
- Intrarticular
  - .Glucocorticoids
  - Hyaluronan
- Topical
  - Capsaicin
  - Methylsalicylate

1.4.1 Physical therapy

The use of physical therapy in the treatment of OA is somewhat controversial. Until relatively recently, exercise was thought to aggravate symptoms and to hasten disease progression (Ytterberg et al. 1994). Patients were instructed to rest an inflamed joint and to avoid weight-bearing activity. However, more recent opinion is that exercise therapy can be both effective and safe in an elderly arthritic population (van Baar et al. 1999; Minor, 1996; Semble et al. 1990).

Exercise therapy for knee OA generally falls into two categories: 1) muscle strengthening (particularly the quadriceps muscles) and 2) aerobic conditioning (Ytterberg et al. 1994). Both forms of exercise are reported to result in functional improvement and pain reduction in patients with knee OA (Ettinger et al. 1997; Kovar et al. 1992). The ideal combination of aerobic and quadriceps strengthening exercises is currently unknown, although it seems likely that activities that can most easily be built into existing lifestyles will prove to be most beneficial. The wide variety of exercise programmes seen to date hinders direct comparison and further research is required in establishing the most effective and safe exercise programme (Maurer et al. 1999; van Baar et al. 1999).

Whilst exercise is now generally accepted as beneficial in the treatment of OA, this belief has been founded on relatively little scientific evidence. Many of the

primary studies are limited by poor methodology. With a few exceptions, almost all early studies have been short-term (<16 weeks). They have frequently been uncontrolled, have been based on small sample sizes and have failed to conduct intent-to-treat analysis (van Baar et al. 1999; Marks, 1993). In addition, the psychosocial aspects of delivering an exercise intervention have been relatively ignored. However, the last 3 years have seen a considerable increase in the number of well-conducted, and informative studies. A summary of recent exercise studies for the treatment of knee OA is presented (Table 7). With the exception of the Kovar et al. study (1992), all have been reported within the last 3 years and represent a considerable advance in our understanding of the possible impact of exercise therapy in the treatment of knee pain and knee OA. Nevertheless, most studies have still been short-term in duration (excluding the Ettinger study in 1997), have involved intensive exercise programmes (usually supervised exercise, 3 times per week) and have employed strict inclusion criteria. Only one study employed a pragmatic approach, with realistic treatment provision, intent-to-treat analysis and broad inclusion criteria (O'Reilly et al. 1999). This study was of 6-month duration but did not control for the psychosocial aspects of exercise provision.

Table 7 Summary of recent exercise studies.

Authors	Subjects	Interventions	Duration	ITT analysis	Adherence	Impact on knee pain	Comments
Deyle et al. (2000) USA study (Army medical centre)	83 patients who were eligible for military healthcare Inclusion criteria: • ACR criteria for knee OA	Manual physical therapy and supervised exercise (n = 42) Placebo treatment – subtherapeutic ultrasound (n = 41)	Interventions delivered in 8 sessions (4 weeks), assessed at 24 months	No	Not reported	Total WOMAC score including pain, stiffness and physical function. Exercise = 36% improvement Placebo = 12% improvement	Individual treatment schedule used. Study population and medical facilities possibly not representative of wider population
O'Reilly et al. (1999) British study	191 community-based subjects aged 40-80 years Inclusion criteria: • Self-reported knee pain	Daily home-exercise (4 treatment sessions) (n = 113) No intervention (n = 78)	6 months	Yes	Not reported	Exercise = 22.5% improvement Control = 6.2% improvement	Pragmatic study No psychosocial control
Maurer et al. (1999) USA study	113 physician referred patients aged 50-80 years Inclusion criteria: • ACR criteria for knee OA • Knee pain for ≥3 months • X-ray grade ≥1 • No OA medication other than oral NSAIDs or analgesics	Supervised strength training (3 times / week) (n = 57) Education (4 lectures) (n = 56)	8 weeks of intervention, assessed at 12 weeks	No	Not reported	Exercise = 36% improvement Education = 22% improvement	Treated most symptomatic knee only Lacked a no intervention control group Limited sample size

Table 7 (continued).

Authors	Subjects	Interventions	Duration	ITT analysis	Adherence	Knee pain	Comments
van Baar et al. (1998) Dutch study	201 GP referred patients aged 40-85 years Inclusion criteria: • ACR criteria for knee or hip OA	Individual physiotherapy (1 to 3 times / week depending on pain) + GP education (n = 99) GP education (n = 102)	12 weeks	Yes	91%	Exercise = 46% improvement Education = 13% improvement	Not possible to isolate patients with knee OA in results Expensive individual physiotherapy
Ettinger et al. (1997) USA study	439 community-based subjects aged ≥60 years Inclusion criteria: • Self-reported knee pain. • Difficulty with ≥1 activity of daily living • Tibiofemoral OA (grade not specified)	Aerobic or resistance exercise (3 months supervised 3 times / week, followed by 15 months home exercise, supported by visits and phone calls) Education (3 group sessions followed by regular telephone contact)	18 months.	Yes	85% at 3 months 70% at 9 months 50% at 18 months	Aerobic exercise = 12% improvement over education Resistance exercise = 8% improvement over education Education = not reported	1st long-term study Intensive programme (unlikely to reflect actual treatment provision in community) Lacked a no intervention control group
Bautch et al. (1997) USA pilot study	34 patients recruited from the community and hospital clinics aged ≥58 years Inclusion criteria: • ACR criteria for knee OA	Exercise (3 times / week) + education (n = 17) Education (weekly) (n = 17)	12 weeks	No	Not reported	Exercise = 37% improvement Education = 42.5% worse	Exercise participants had more severe disease and higher BMI at baseline

Table 7 (continued).

Authors	Subjects	Interventions	Duration	ITT analysis	Adherence	Knee pain	Comments
Kovar et al. (1992) USA study	102 hospital patients aged ≥40 years Inclusion criteria: • Radiographic OA • ≥4 month history of knee pain • NSAIDs used ≥ 2 / week.	Hospital-based supervised walking (3 times / week) + education (n = 51) Routine care (n = 51)	8 weeks	No	92%	Exercise = 27% improvement. Control = 2% improvement	Intensive programme of short-term duration
Sullivan et al. (1998) USA study	52 subjects from earlier study (Kovar et al. 1992)	Follow-up of earlier study Walking (n = 29) Control (n = 23)	12-month follow-up	No	Returned to baseline	Returned to baseline	Limited sample size but useful follow-up data

Whilst the majority of studies have concentrated on the effects of muscle strength training, improved health status has also been reported for aerobic exercise, which has the advantage of being easily incorporated into daily life. One influential study (Kovar et al. 1992) described a group of hospital and GP referred patients who had radiographic evidence of knee OA, self-reported knee pain and regularly used non-steroidal anti-inflammatory drugs (NSAIDs). The initial study was for an 8-week period and involved both supervised fitness walking and supportive fitness education. Controls for the study received normal medical care, with no further intervention from the investigators. This study was able to demonstrate clinically meaningful improvement in walking distance, functional status, pain and medication use in those subjects in the fitness walking group compared with controls. However, a follow-up study showed that the majority of patients failed to maintain their regular walking activity after one year(Sullivan et al. 1998). As a result, the functional benefits associated with the programme were lost. It is clear that future work needs to examine ways in which patients can become more pro-active in their own treatment regime, and to establish factors that may influence future adherence (Clark and Gong, 2000; Jensen and Lorish, 1994).

A study that addressed the issue of adherence examined exercise beliefs in relation to an individual's likelihood to participate in exercise (Gecht et al. 1996). Arthritic subjects aged 27-80 years were asked about their participation in six types of exercise; all of which are commonly recommended for people with OA (e.g. swimming, water exercises, brisk walking, range of motion

exercises). An exercise belief questionnaire was used to assess individuals' beliefs regarding self-efficacy (the extent to which they felt capable of performing an activity), the possible barriers to exercise and the potential benefits of exercise. This cross-sectional survey suggested that those people most likely to exercise 1) believed in the positive benefits of exercise and 2) had higher self-efficacy scores than those who did not exercise.

Both self-efficacy and pain have been identified as mediating factors in effective exercise therapy (Rejeski et al. 1998) and are useful in predicting future adherence (McAuley et al. 1993). Findings such as these support the growing recognition of the importance of cognitive-behaviour programmes in the treatment of OA. Such programmes commonly include exercise therapy as just one element of a wider education programme, and are designed to alter patient's knowledge, behavioural skills, attitudes and emotions (Lorig et al. 1993a) (Lorish and Boutaugh, 1997).

Finally, the attitude of health professionals is worth noting. To date, OA patients have received somewhat conflicting advice with regard to exercise activity. Conflicting advice has been identified as an importance source of misunderstanding between patient and physician and may be an important factor in reduced treatment adherence (Britten et al. 2000). It is clearly important for consistent information to be delivered by GPs, rheumatologists, nurse practitioners and self-help groups (Holman and Lorig, 1997).

1.4.2 Telephone support

Telephone support from health professionals was identified as an effective treatment option in the guidelines for the medical management of OA (ACR subcommittee on osteoarthritis guidelines, 2000). Support and advice from health professionals is of key relevance in assessing the efficacy of exercise therapy, and yet few studies have adequately controlled for the effects of contact with a health professional.

The possible effectiveness of telephone support in relation to OA was first identified by Weinberger and his colleagues over a decade ago (Weinberger et al. 1986). This initial uncontrolled study examined the effect of bi-weekly telephone calls to patients with OA over a period of 6 months and was able to demonstrate significant improvement in functional status.

A subsequent study by Weinberger et al. (1989) expanded on this early work with a large RCT involving 439 subjects. Once again, the study looked at the provision of information and support, with subjects being randomised to one of four treatment groups. These included: a) monthly telephone contact by trained lay-personnel, b) contact with lay-personnel during normal clinic visits, c) combined telephone contact and clinic contact and d) no change to existing treatment. Telephone support was identified as producing significant improvement in both physical function and pain, with a slight additional improvement in psychological health. However, this study was based on a

sample of predominantly black females, of low socio-economic class. The ability to generalise findings to a wider population was therefore limited.

More recently, a study by Maisiak et al. (1996) examined the impact of two different types of telephone intervention in subjects with both OA and RA. This study involved 405 subjects of a more representative demographic mix than was used in the Weinberger study, and extended over a nine-month period. The two telephone treatment arms involved: 1) treatment counselling (designed to increase patient involvement), 2) symptom monitoring (provided social support, but no advice or direct patient involvement). The control group received their normal level of medical care. Once again, an overall improvement in physical health was observed with significant improvements in physical function and pain for the treatment counselling group, (improvements were also seen in the symptom monitoring group, although these did not reach significance at the 5% level).

It would seem that telephone support produces significant improvements in health status, and that the magnitude of this effect may be of some clinical significance. However, the exact mechanism for this improvement is poorly understood. Weinberger et al. found little support for an impact on any of the most obvious intervening factors, including treatment adherence, morale, social support or satisfaction with care (Rene et al. 1992). Nevertheless, limited evidence is available to support the belief that support reduces the stress associated with chronic illness (Weinberger et al. 1990). Others have

suggested that regular contact encourages people to concentrate on improving their functional status (with self-help activities), rather than ignoring health issues (Maisiak et al. 1996).

Regardless of the mechanisms involved, telephone support (from either health professionals or trained lay-personnel) appears to represent an extremely cost-effective method of achieving and maintaining health benefits in OA patients. As such, its further investigation and recognition is certainly warranted.

1.5 Economic evaluation of osteoarthritis

1.5.1 Economic evaluation techniques

Economic evaluation has been defined as:

> *"the comparative analysis of alternative courses of action in terms of both their costs and consequences." Drummond et al. (1997) p. 8.*

This definition includes two key concepts, which are fundamental to any economic analysis. Namely, the inclusion of both costs and consequences, and the concept of the comparison of competing alternatives. These two aspects can be used to identify the type of analysis being undertaken and to distinguish between partial and full economic analyses. This concept is demonstrated more fully in Table 8.

Table 8 Factors used to distinguish the characteristics of different health care evaluations (from Drummond et al. 1997).

Are two or more alternatives compared?	Are both cost and consequences of the alternatives examined?		
	NO		YES
NO	Examines only consequences	Examines only costs	
	PARTIAL EVALUATION	PARTIAL EVALUATION	PARTIAL EVALUATION
	Outcome description	Cost description	Cost-outcome description
YES	PARTIAL EVALUATION	PARTIAL EVALUATION	FULL ECONOMIC EVALUATION
	Efficacy or effectiveness evaluation	Cost analysis	Cost-minimization Cost-effectiveness Cost-utility Cost-benefit

For the purposes of this study, two types of economic evaluation are particularly relevant:

a) cost-effectiveness analysis

b) cost-utility analysis.

Whilst these two forms of analysis are essentially very similar, it is important to recognise the difference between the two, and the potential strengths and weaknesses of each.

1.5.1.1 Cost-effectiveness analysis

Definition: This analysis measures the cost of compared medical treatments in relation to clinical outcomes, which are measured in physical units (e.g. life-years saved, number of operations performed or changes in functional ability). Results are presented as a ratio statistic in terms of cost per unit of outcome.

Cost-effectiveness analysis is a useful tool in comparing the health consequences of treatments designed to elicit similar health outcomes. Its primary use is in estimating the incremental costs of providing one intervention over another, rather than in attempting to value outcomes per se. Cost-effectiveness analysis is not able to make comparisons between evaluations in the same or different treatments and disease areas where the measures of outcome differs. For example, it is of little use comparing the consequences of open-heart surgery (possibly in terms of life-years saved) with that of knee replacement surgery (possibly in terms of physical disability or pain). In order

to include the benefits of a range of relevant beneficial and adverse outcomes in one measure cost-utility analysis has developed.

1.5.1.2 Cost-utility analysis

Definition: This analysis measures the cost of medical treatments in relation to quality-of-life (e.g. quality-adjusted life-years, or QALYs). Results are presented in terms of cost per QALY.

Cost-utility analysis is based on utility theory and measures the expected gain (or utility) from the consumption of a good or service. In terms of health care, this equates to the value placed on health gains derived from the use of health care interventions. Fundamental to cost-utility analysis is the concept of the quality-adjusted life-year (QALY). The advantage of the QALY is that it combines the quality of life (morbidity) with the quantity of life (mortality) into a single measure.

The immediate appeal of cost-utility analysis is that it provides a common 'currency' (QALYs) with which to compare disparate treatments. In this way, decisions can be facilitated regarding the appropriate allocation of funds across a range of treatments, whilst avoiding the pitfalls of trying to place a monetary value on intangible items such as pain and suffering (the major difficulty faced by cost-benefit analysis). Unfortunately, it is this very comparability which has led to one of the major debates surrounding cost-utility analysis; namely the

use of 'cost per QALY gained' league tables. In such tables items are ranked according to their cost per QALY. Rank order, rather than patient need governs recommendations for treatment priority. Such methods have caused controversy in the past and whilst league tables have a unique role to play in health policy decision-making, they should nevertheless be treated with caution (Gerard and Mooney, 1993). In particular, doubt has been cast on the comparability of QALY measures when findings are based on poorly executed and methodologically varied primary studies. The relative insensitivity of some generic utility measures also means that interventions resulting in only small changes in perceived quality-of-life might be dismissed as ineffective. Whether little difference in utility in the presence of clinical improvements reflects insensitivity in the instrument or changes that the patient or society do not value is still a matter of debate.

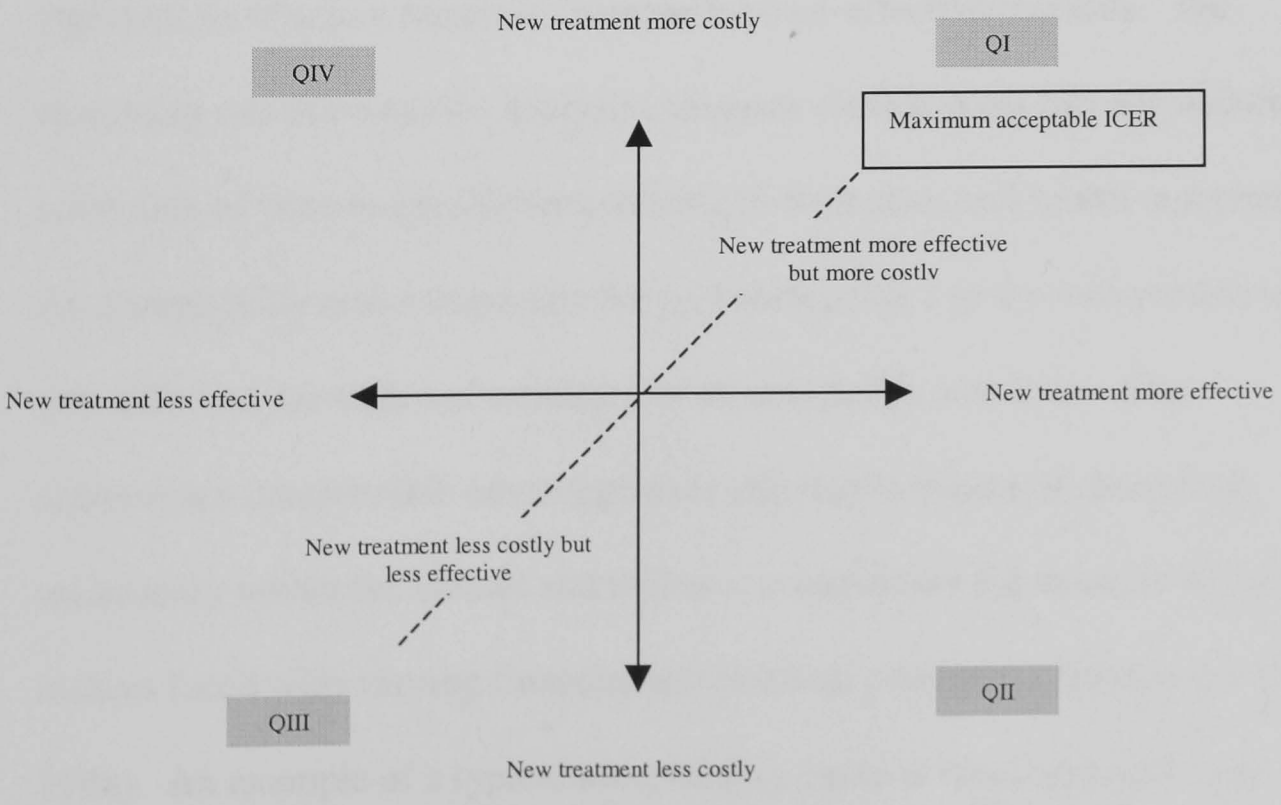
Despite these limitations, cost-utility analysis has a unique role to play in informing policy decision making and has become increasingly recommended by health policy decision-makers.

1.5.2 Presentation of cost data

1.5.2.1 Cost-effectiveness plane

An indication of cost-effectiveness (CE) is often presented using the cost-effectiveness plane, as shown in Figure 6. The CE plane is divided into four quadrants, which represent four possible situations in relation to the relative cost and health outcomes of a new therapy compared to standard care. In quadrants II and IV, one therapy is simultaneously cheaper and more effective than the other and is said to dominate. In reality, most interventions fall within either quadrants I or III. In these cases, a decision must be made. In quadrant I the new treatment is considered to be more effective, but more costly (the most common scenario). In quadrant III the new therapy is less costly, but is also less effective.

Figure 6 The cost-effectiveness plane (taken from Briggs & Fenn, 1998).



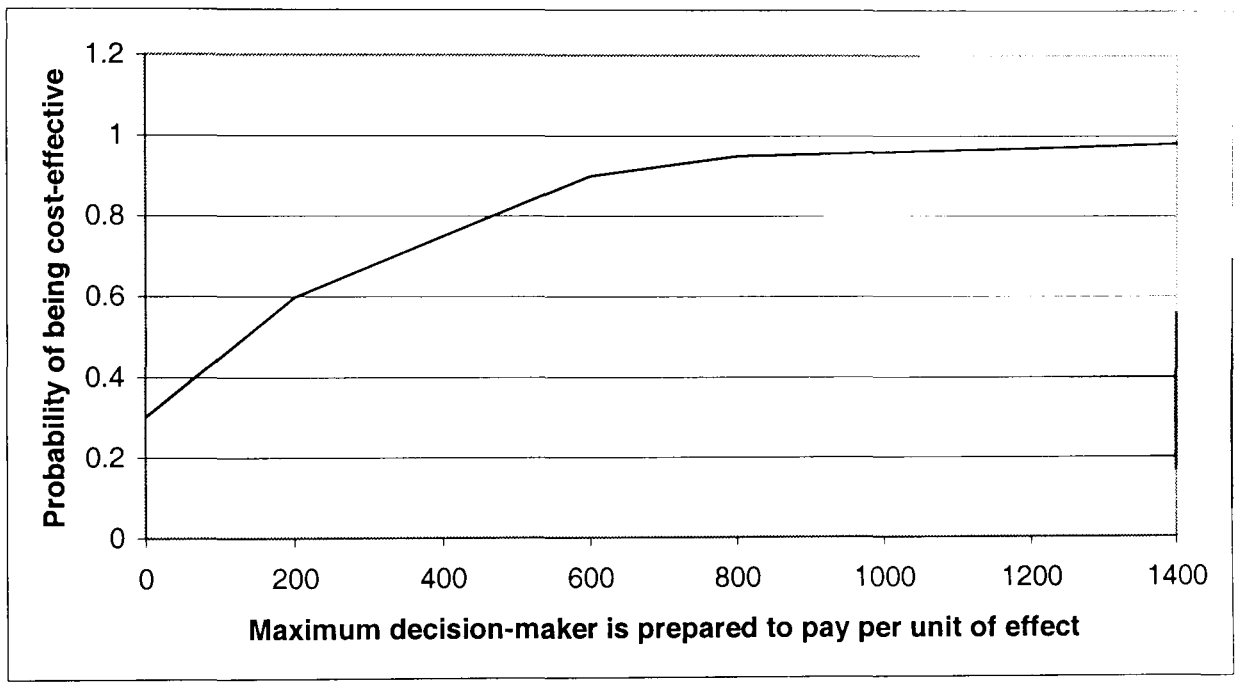
In order to make a decision as to the cost-effectiveness of a given intervention, it is necessary to identify an acceptable value (or criticial ratio) for the incremental cost-effectiveness ratio (ICER = Δ cost / Δ effect). Below this value a therapy may then be labelled as cost-effective. Such a value is represented by the dashed line on Figure 6. This line has its origin at the point where the new therapy is equivalent to the old therapy. For points lying below the line, new interventions are labelled as being cost-effective. For points above the line, the new therapy should be labelled as ineffective. This line or "acceptability surface" can be used to calculate the probability that the ICER is under a certain acceptable limit and is presented in the form of an acceptability curve (van Hout et al. 1994).

1.5.2.2 Cost-effectiveness acceptability curves

Acceptability curves were first described by van Hout et al. (1994), and represent an intuitive means of interpreting cost-effectiveness data. The increasing use of economic analysis alongside clinical trials has allowed the collection of patient-specific data relating to both costs and health outcomes. An acceptability curve illustrates the probability that a given intervention is cost-effective for different estimates of an acceptable cost limit. This represents a considerable advantage over alternative means of describing uncertainty within the dataset and makes it a useful tool for medical decision-makers faced with varying financial and political constraints (Briggs and Fenn, 1998). An example of a typical acceptability curve is illustrated in Figure 7. In

this example, there is a 80% probability that the intervention will be cost-effective if the provider is willing to pay over £480 per unit of effect. Probability at the 50% level (£140) represents the point estimate of the mean ICER that is traditionally reported.

Figure 7 Example of a typical acceptability curve.



1.5.2.3 Sensitivity analysis

Whilst acceptability curves provide an indication of variability in the dataset, there are other areas of uncertainty inherent in the process of gathering cost data for cost-effectiveness analysis. The usual means of exploring these areas of uncertainty is through sensitivity analysis. This may include uncertainty regarding unit costs, methodological considerations or issues of generalisability (Briggs and Fenn, 1998). Sensitivity analysis involves the systematic application of alternative estimates relating to parameters included in the analysis (including uncertainty relating to both costs and outcomes). In this

way the impact of assumptions made during the analysis process can be quantified and the robustness of the resulting cost-effectiveness ratio can be explored. The choice of parameters to be included in the analysis should be justified, as should the plausible range of values employed (Briggs et al. 1994).

A recent review suggested that appropriate sensitivity analysis was still lacking from many economic evaluations published in the literature (Briggs and Sculper, 1995). Whilst general agreement now exists to suggest that sensitivity analysis should be conducted (Drummond et al. 1996), few guidelines exist as to the exact nature of the sensitivity analysis required (Jefferson et al. 1996). Several forms of sensitivity analysis have been reported. These include one-way; multi-way; extreme; threshold; and probabilistic sensitivity analysis. The simplest and most common form of analysis is *one-way* or *univariate sensitivity analysis*. This examines the impact on the C/E ratio of varying the estimated value of one parameter at a time. One-way sensitivity analysis is commonly used, but has been criticised for being too simplistic in nature; particularly as it ignores the possible interaction of different parameters (Johnston et al. 1999). In order to address this issue, *multi-way analysis* can be performed. This involves the systematic manipulation of several parameters at one time. *Extreme sensitivity analysis* is used to present the possible 'best' and 'worst' case scenarios by combining the most extreme estimates for each parameter. It has been argued that this method is only useful if the results are very insensitive to change. Otherwise, a broad (and possibly unrealistic) band of uncertainty may be identified (Gold et al. 1996). *Threshold analysis*

requires the manipulation of parameters to the point whereby the most cost-effective treatment is no longer dominant. Finally, *probabilistic sensitivity analysis* involves the use of Monte Carlo simulation techniques to address areas of uncertainty in the dataset. Values are selected at random from a given distribution to generate the value of a parameter, over several iterations. In this way various parameters can be considered across a range of plausible values at one time (O'Brien et al. 1994).

1.5.3 Cost analysis within rheumatology

The last decade has seen an increase in the total number of economic evaluations within the medical literature (Elixhauser, 1993). Despite this increase, several reviews have pointed to the relatively poor quality of economic research (Rothfuss et al. 1997; Adams et al. 1992; Udvarhelyi et al. 1992). Udvarhelyi et al. (1992) compared studies published from 1978-1980 with those published from 1985-1987. They found little evidence for any improvement in quality over time, although articles published in general medical journals were more likely to use appropriate analytical techniques than those published in medical subspecialties. A review of economic analyses conducted alongside RCTs between 1966 and 1988 (Adams et al. 1992) revealed that only 121 of over 50,000 studies (0.2%) included economic analysis. Of those studies involving economic analysis, the most common deficiencies were the inappropriate allocation of overheads, a lack of sensitivity analyses and the presentation of costs and benefits in a disaggregated form.

Within the field of rheumatology several more recent reviews have been published. Ferraz et al. (1997) concluded that well-conducted economic evaluation in the discipline was still lacking. Following an extensive MEDLINE search (covering the period 1966 – 1995), they found just 13 full economic evaluations relating to OA (8 of which investigated the use NSAIDs. Large gaps existed in the investigation of many aspects of the treatment and management of OA. In addition, the poor comparability of those studies that did exist, meant that inconsistent results were difficult to interpret.

More encouragingly, a review of cost-effectiveness analyses conducted during the year 1996-1997 suggested an improvement in the quality of economic analysis within the field (Maetzel et al. 1998). These investigators identified the major shortcoming of more recent studies to be the over-reliance on estimated costs, rather than on prospectively collected resource use data.

One explanation for an improvement in the quality of studies in recent years is the establishment of explicit guidelines for conducting economic analysis (Ruchlin et al. 1997; Russell et al. 1996; Weinstein et al. 1996; Drummond et al. 1996). It is hoped that the wider acceptance of such guidelines will greatly improve the reliability and generalisability of results across all disciplines. A composite of the guidelines is outlined in Table 9.

Table 9 Summary of the guidelines for economic analysis (adapted from Drummond & Jefferson, 1996; Weinstein, 1996 and Ruchlin, 1997).

1. **Clear specification of the question:**
   Alternative clinical interventions should be stated.
2. **Choice of an explicit point of view:**
   Societal, health provider or individual?
3. **Description of medical effectiveness**:
   Source(s) and reliability of data.
4. **Appropriate identification of costs:**
   Direct medical costs, indirect costs and intangible costs.
5. **Presentation of both input and output in physical units.**
6. **Identification of credible unit costs**:
   Distinction should be made between fixed and variable costs.
7. **Discounting:**
   Adjusting future costs/benefits to present day values.
8. **Incremental analysis**:
   Difference between an intervention and the next best alternative should be presented for both costs and consequences.
9. **Sensitivity analysis:**
   Identification of uncertainties and bias. Are the study results sensitive to change?
10. **All issues included in results**:
    Difficulties, assumptions and ethical considerations.

1.5.4 Economic impact of osteoarthritis

Until quite recently, the socio-economic impact of OA was considered to be relatively slight (particularly in comparison with RA, which incurs higher direct medical costs and has greater associated disability). However, the markedly higher prevalence of OA (8.7%-12.3% for OA versus 0.2%-1% for RA) means that the cost to the health provider is nearly seven times greater for the treatment of OA than it is for the treatment of RA (Lanes et al. 1997). The economic impact of musculoskeletal disorders has been estimated to be as great as the economic consequences of cancer (Badley, 1995b), and yet cost-of-illness studies for OA are markedly lacking (Huijsman, 1995). The majority of studies to date are based on American datasets and deal either with musculoskeletal conditions in general (Yelin and Callahan, 1995), or concentrate exclusively on rheumatoid arthritis (Cooper, 2000; van Jaarsveld et al. 1998; Rothfuss et al. 1997). To isolate the costs incurred by OA is difficult. Nevertheless, several recent studies have attempted to address this issue. For ease of comparison, all figures are quoted with 1996 £ sterling equivalent values in brackets. Conversions were made using the current exchange rate of £0.69 per US$ and adjusted for inflation using the hospital and community health services pay and prices index.

Lanes et al. (1997) looked at the provision of medical services for OA patients over the period 1993 to 1994. They reported average direct medical costs for the treatment of OA related conditions of $543 (1996, £394) per patient per year. Almost half of this amount was accounted for by hospital care (46%), despite only 5% of OA patients having received such care. The distribution of

costs was thus highly skewed. The majority of patients incurred costs of less than $400 (1996, £290) per year.

Other work by Gabriel et al. has contributed greatly to our understanding of the economic impact of OA (Gabriel et al. 1997a; Gabriel et al. 1997b; Gabriel et al. 1995). In particular, the importance of examining all medical costs rather than those attributable to OA alone has been highlighted. OA patients show significantly higher direct medical costs for a range of conditions (respiratory, cardiovascular, gastrointestinal, neurological, psychiatric and general medical care) than non-arthritic controls (Gabriel et al. 1997a). Comorbidity is known to be high amongst OA patients, although exact reasons for this remain unclear. Some conditions (such as diabetes) may be associated with the aetiology of OA, whilst others (such as gastrointestinal complications) may stem from OA treatments themselves (Hochberg et al. 1989).

The impact of indirect costs and non-medical expenditure is also high. (Gabriel et al. 1997b; Gabriel et al. 1995; Yelin and Callahan, 1995). OA subjects are more likely than age-matched controls to report a reduction in work hours due to illness (10.5% of OA and 1.7% of controls reported reduced hours), and are more likely to have taken early retirement (13.7% of OA and 3.4% of controls) (Gabriel et al. 1995). This finding is confirmed by Hochberg et al. (1995) who identified OA as being the second most common cause of early retirement in the US (>5% per year).

Gabriel et al. also noted that OA patients need high levels of informal care (help from family and friends) as a result of their condition, and that they incur additional expenditure for the purchase of equipment (medical equipment, assistive devices and the installation of ramps or rails). Disregarding wage losses (which were excluded from analysis because of large differences in hourly wages across the 3 groups) average indirect and non-medical expenditure for 1992 was $593 (1996, £445), $282 (1996, £211) and $57 (1996, £43) for RA, OA and non-arthritic controls respectively.

In summary, OA inflicts a sizeable economic burden on society. Whilst direct medical costs can be relatively modest in the majority of cases, the large number of people affected ensures that the health service incurs a substantial cost. Analysis of the indirect costs of arthritis suggests that the wider burden on society is even greater.

1.5.5 Intangible costs associated with osteoarthritis

Intangible costs reflect the cost of pain, suffering and disability incurred by OA sufferers and their family. By their very nature, intangible costs are difficult to value in monetary terms. Nevertheless, consideration of the impact of such costs on daily life is important.

Until fairly recently, the psychosocial impact of OA had been relatively neglected. However, survey data have revealed considerable levels of pain,

limited functional capacity and social isolation (Hochberg et al. 1995; Badley et al. 1994; Davis et al. 1991).

The 1990 Ontario Health Survey contacted 45,650 individuals aged 16 and over (Badley, 1995a). Their findings showed OA to be the primary cause of long-term disability in Canada (2.3%); ahead of circulatory disease (1.4%). Disability was higher in women (3.8%) than men (1.6%), and showed a marked increase with age (from 0.1% for the 16-24 age group to 20.6% for those aged 85 years and older). Of those reporting OA associated disability, three quarters were dependent on others for help at least occasionally, and almost half needed help at least every few days. These findings were mirrored in the degree to which people with disability suffered from social isolation, with 13.2% never visiting friends or relatives.

1.5.6 Cost of knee osteoarthritis

Given the difficulty in isolating the economic impact of OA from other musculoskeletal conditions, it is possibly not surprising that cost data relating specifically to the knee joint are lacking. The relative importance of knee OA in dictating health service resource use compared with other forms of OA such as back or hip arthropathy requires further investigation.

1.5.7 Economic evaluation of treatment provision

Although arthritis has serious health consequences, Rothfuss et al. reported that

> *"the gap between the importance of the socioeconomic effects of RA and OA and the research conducted in this field is considerable." (Rothfuss et al. 1997 p771).*

Following an extensive MEDLINE search, they found 44 studies that presented original cost data (the majority of which concentrated on RA rather than OA), only 6 of which had performed an economic evaluation of the provision of a rheumatology service, and no cost-utility analyses. Clearly the need for well-directed and thorough economic evaluation is of paramount importance if rheumatological services are to compete for finite resources within the health sector.

Existing cost-effectiveness data concentrates primarily on either the cost-effectiveness of surgical management (Chang et al. 1996; Liang et al. 1986) or on treatment with prescribed drugs (Gabriel, 1995; Paakkari, 1994; Hillman and Bloom, 1989). Whilst these areas are clearly important elements in the treatment of arthritis, patient education, telephone support, weight loss, physical therapy and occupational therapy should not be ignored. It is these aspects of care which are of greatest relevance to the current study and which have been relatively neglected in the literature to date.

As previously discussed, Rene et al. (1992) and Weinberger et al. (1989) reported reduced knee pain and improved physical health following monthly telephone calls by non-medical staff. A subsequent cost-effectiveness analysis Weinberger et al. (1993) revealed telephone support to be highly cost-effective, largely as a result of its extremely low implementation costs ($14.88 per person, 1996 £13). No differences were found in levels of health care utilisation. The authors were unable to provide an accurate comparison with any alternative form of treatment, such as an exercise programme, although they did hypothesise that telephone support and physical therapy would probably have similar costs per unit of effectiveness gained.

Other studies have concentrated on the provision of information and self-management with a view to encouraging patients to access health care systems more appropriately. Lorig et al. reported the Arthritis Self-Management Programme (ASMP) as being able to produce sustained improvement in indicators of pain and depression, whilst reducing physician visits by up to 40% (Lorig et al. 1995). Estimated savings over a 4-year period were of the order of $648 (1996, £573) per RA patient and $189 (1996, £167) per OA patient (Lorig et al. 1993b). Similar findings were reported by (Cronan et al. 1997a), who examined the impact of social support, education or a combination of the two in reducing health care costs of patients with OA. They reported potential annual savings of $1,156 (1996 £818) per person, with no obvious decrease in health status. The markedly higher potential saving demonstrated by the latter study partially reflects the characteristics of the study population.

This was a group of extremely high service users (mean number of contacts during the one year baseline period was 16.9 visits). In addition, control subjects showed a significant increase in the number of inpatient days during the study period. This produced incremental costs in excess of 100% of baseline after 2 years (compared with increases of between 23 and 31% for the intervention groups). The interpretation of cost data based on relatively small changes in high cost events such as these should be treated with great caution.

A recent British study, which assessed the cost-effectiveness of health education for the treatment of knee OA in a primary care-based setting, suggested that education programmes might not be cost-effective (Lord et al. 1999). These investigators failed to observe any improvement in health outcomes after one year. Furthermore, the cost of delivering the education programme (£140 per person) was not offset by any reduction in the utilisation of health service resources.

Studies investigating the cost-effectiveness of physical therapy for the treatment of rheumatological conditions are less common. One study compared the cost-effectiveness of providing group physical therapy in addition to individualised home exercise in patients with ankylosing spondylitis (Bakker et al. 1994). Group therapy was provided in groups of 12 patients and consisted of 1 hour of physical training, followed by 1 hour of sporting activities (e.g. volleyball or badminton) and 1 hour of hydrotherapy. The cost of delivering the home exercise programme was fixed at zero since both groups

received the same intervention. Outcomes were assessed at 9 months and the final cost-effectiveness analysis was based on data for those patients who returned a completed cost diary at the end of the study (77% of the original sample).

The cost of providing group therapy in addition to home-exercise was approximately $531/patient/year ($44 per month, 1996, £33). This consisted of $177 (1996, £133) for the sports facilities, $256 (1996, £192) for the therapist and $98 (1996, £74) for materials and equipment. During the period of the study, direct medical costs were reduced in both treatment groups. This was by $122 (1996, £92) more for those allocated to group therapy than for those who received home exercise. The significance of this finding is difficult to determine since multiple significance tests were performed relating to 18 different types of service use. In addition, the dominance of high cost, but relatively infrequent events (such as inpatient stays), was again noted. Nevertheless, at the end of the 9-month trial, 75% of the patients wanted to continue with the programme and were willing to pay for it.

Economic evaluation of a community-based exercise programme for the treatment of low back pain has been reported (Moffett et al. 1999). This study assessed the impact of providing group exercise sessions led by a physiotherapist (8 sessions over a period of four weeks). The cost of delivering the exercise programme was estimated to be £25.20 per person treated (1996 £ sterling). Patients in the intervention group tended to use fewer healthcare

resources than those allocated to the control group (mean difference £148 per patient). However, this difference was not statistically significant and wide confidence intervals were reported (-£442 to £146). The possible impact of exercise therapy on indirect costs was also highlighted. Patients allocated to the control group reported almost twice as many days off work due to back pain than those in the exercise group (607 days off versus 378 days over the 12-month study period).

In conclusion, it would appear that exercise therapy could be used in order to provide cost-effective patient care. However, data relating to physical therapy for the treatment of knee OA are still lacking. The scarcity of reliable and well-conducted economic research within the field of rheumatology is particularly marked and should be urgently addressed. Emphasis on the potential costs and benefits of all non-pharmacological interventions is urgently needed.

1.6 Summary

- Knee pain is an extremely common condition, which is associated with considerable morbidity
- Discordance exists between the presence of radiographic knee OA and knee pain
- The use of case criteria based on the presence of knee pain is important for epidemiological research, since it is symptomatic OA that reflects the community burden of the condition
- The efficacy of exercise therapy for the treatment of knee pain remains unclear
- Social support from health professionals, or lay personnel, has been associated with positive health benefits. It is important to recognise psychosocial factors in determining the efficacy of physical therapy
- The economic consequences of the conservative management of knee pain have been largely ignored

1.7 Contribution of current study

This study describes a large, prospective randomised controlled trial (RCT), which examines the cost-effectiveness of a home-based exercise programme in relieving the severity and disability of knee pain. Exercise therapy is compared with monthly telephone support, a placebo health-food product or no intervention. Health outcomes are measured over a two-year period and results presented in terms of both cost-effectiveness and cost-utility ratios.

The investigation of any complex health intervention presents methodological difficulties. This may serve to explain the apparent dearth of relevant research in the field (Dieppe and Szebenyi, 2000). Nevertheless, recent focus groups have revealed a disparity between the research that is being carried out (namely drug trials), and that which consumers feel to be necessary (further investigation of non-pharmacological treatments) (Dieppe et al. 1999). It is hoped that the current study goes some way to addressing this need.

1.7.1 Study design

Previous studies investigating the efficacy of physical therapy for the treatment of knee OA have been limited by methodological constraints. The current study addresses some of these issues through a large-scale, randomised controlled trial (RCT). The study is unique in that it employs a randomised factorial design with four possible treatment arms: home-based exercise therapy, monthly telephone support, a placebo health-food product and no

intervention. Such a design allows greater understanding of the mediating factors associated with improved health outcomes following physical therapy (including the impact of social support and a possible placebo effect). The failure to include a no intervention control group in addition to education or social support control groups has been a major weakness of earlier studies

With the exception of the Ettinger study (1997), which examined outcomes after 18 months, the long-term impact of physical therapy for the treatment of knee OA has not been explored. The current study examines outcomes prospectively over a 2-year period and is thus able to address issues of treatment adherence and possible adverse side effects over an extended time period.

1.7.2 Pragmatic nature of the trial

Throughout the study a pragmatic approach has been adopted. This means that limited exclusion criteria have been employed, study interventions are provided in addition to existing levels of care, all treatments are provided with a minimum of input from the research team, and results have been analysed on an intent-to-treat basis.

Pragmatic studies are particularly appropriate when economic data is collected concurrently (Langley, 1995). In attempting to isolate the effectiveness of a particular treatment, investigators frequently eliminate possible confounding

factors such as comorbidity, poor treatment adherence and treatment error. Using such data as the basis for cost-effectiveness estimates presents clear difficulties and it is hoped that the pragmatic nature of the current study avoids such problems.

1.7.3 Case criteria

As this was a community-based knee pain study, inclusion criteria were based solely on self-reported knee pain (using the NHANES pain question Davies et al. 1992). In this way, it has been possible to circumvent the debate surrounding the appropriate definition of knee OA (radiographic evidence of change versus symptom reporting). It is hoped that subjects enrolled in the study are broadly representative of symptomatic patients in a primary care setting.

1.7.4 Concurrent economic evaluation

To develop economic analysis alongside a RCT has distinct advantages and its use has been promoted in recent years (Griffiths et al. 1995; Adams et al. 1992). As yet, little is known regarding the cost-effectiveness of physical therapy and/or social support. The availability of prospectively collected cost data provides a unique insight into the economic impact of these treatments, and allows an examination of the economic impact of both positive and negative health consequences.

1.8 Summary of Study Design

Study Design	Aims and objectives
Chapter 2: **Intervention study - RCT** **(n = 786)**	1. To determine the prevalence of knee pain in adults aged ≥45 years. 2. To determine whether regular quadriceps muscle exercise improves long-term outcomes in subjects with knee pain 3. To determine the importance of social support in explaining positive health outcomes 4. To isolate the factors most closely associated with positive outcomes
Chapter 3: **Cost-of-illness** **(n=759)**	1. To assess the cost of knee pain in the study sample 2. To establish some of the factors associated with the accessing of health facilities
Chapter 4: **Economic Evaluation** **(n = 759)**	1. To perform a cost-effectiveness analysis based on outcome measures obtained from the intervention study 2. To perform a cost-utility analysis in which outcomes are measured in Quality-Adjusted Life-Years

2 Intervention study

2.1 Aims and objectives

This intervention study, which provided effectiveness data for the subsequent economic analysis, had four primary objectives.

1. To determine the prevalence of knee pain in adults aged ≥45 years.
2. To determine whether regular quadriceps muscle exercise improves long-term outcomes (symptoms and function) in subjects with knee pain.
3. To determine the relative contribution of psychosocial factors in explaining these health outcomes.
4. To isolate the factors most closely associated with positive outcomes.

2.2 Method

2.2.1 Ethics

All aspects of these studies were approved by the City Hospital and Nottingham University Local Research Ethics Committees. Support from participating GPs was made clear in the initial contact letter and informed consent was obtained for participation in the trial prior to initial assessment. In addition, signed consent was obtained for the accessing of GP notes as part of the economic evaluation (chapters 3 and 4). Copies of the relevant consent forms are appended (Appendix 1).

2.2.2 Study population

The study population consisted of men and women (aged 45 years and over), who were registered at one of two general practices in the Nottingham area.

- Practice A - Torkard Hill Medical Centre, Hucknall. (List size: 11,967).
- Practice B - Arnold Health Centre, Arnold. (List size: 15,000).

Both practices are situated on the northern outskirts of Nottingham.

A study population aged 45 years and over was chosen in order to reflect general prevalence patterns for knee OA (Croft, 1990). No upper age limit was set in order to increase the generalisability of study findings.

Prior to the distribution of questionnaires, recruitment lists were examined by GPs according to the following exclusion criteria:

- Age <45 years.
- Terminally ill patients (with a life expectancy of less than 2 years).
- Psychiatric history leading to an inability to give informed consent.
- Patients unable or unwilling to give informed consent (including those living in nursing homes).
- Non-residence in the Nottingham area.

This procedure resulted in a potential study population of approximately 4,540 (practice A) and approximately 6,500 (practice B).

A list of eligible subjects was obtained for all patients aged 45 years and over as of 1st January 1996 for practice A and from 1st July 1996 for practice B, (recruitment for practice B was started 6 months after recruitment for practice A). Questionnaires were subsequently distributed to all patients from practice A and to 73% of patients from practice B.

2.2.3 Sample size

The sample size for the postal survey was based largely on the need to ensure adequate numbers of knee pain positive volunteers for the subsequent RCT (n = 800). This yielded sufficient numbers for the intervention study to detect a 20% difference in WOMAC pain scores with greater than 90% power, based on a prevalence of knee pain of 25% (McAlindon et al. 1992). These power calculations were supported by data from a recent survey in Nottingham, which provided confirmation of a similar age-stratified prevalence of knee pain (O'Reilly et al. 1998).

2.2.4 Questionnaire

The questionnaire used in the postal survey was based on one used in an earlier study (O'Reilly et al. 1998). A full copy is appended (Appendix 2). A covering letter was sent with each questionnaire. This outlined the nature of the trial and encouraged volunteers to seek assistance should they have problems completing the questionnaire. It also made clear that participation in the trial was being sought with the full support and understanding of their GP.

2.2.5 Distribution of questionnaires

Questionnaires were distributed in batches of 500 at three weekly intervals with a pre-paid envelope enclosed. Questionnaires for practice A were posted between December 1995 and April 1996. Those for practice B were distributed between May 1996 and November 1996. A reminder and second questionnaire

- Age <45 years.
- Terminally ill patients (with a life expectancy of less than 2 years).
- Psychiatric history leading to an inability to give informed consent.
- Residence in a nursing home.
- Non-residence in the Nottingham area.

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Treatment arms consisted of six groups including a combination of four factors.

a) physical therapy (home-based quadriceps strengthening and walking)

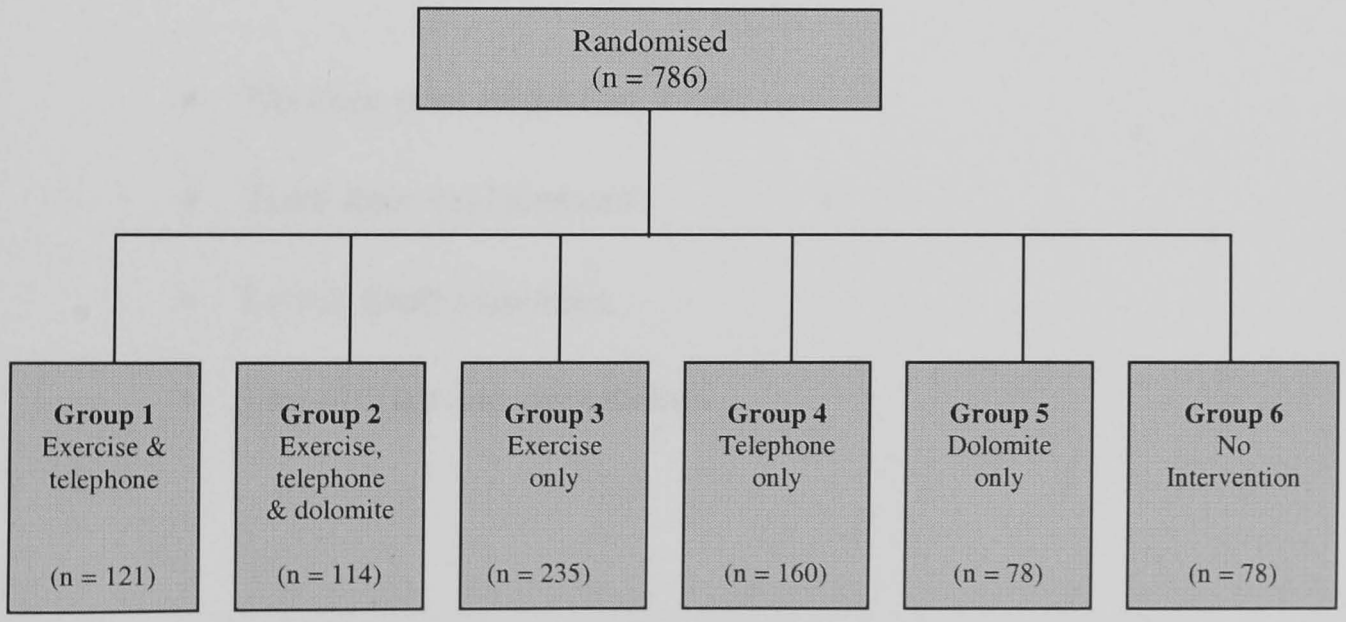
b) monthly telephone support

c) a placebo health-food product

d) no intervention.

Such a design allowed comparison by group (groups 1 – 6) or by factor (physical therapy, telephone support, placebo or nothing). It also provided some exploration of the possible interaction of treatment effects (Figure 8).

Figure 8 Summary of treatment allocation.



2.2.7 Subjects

Subjects for the intervention study were recruited using the initial postal questionnaire. Entry into the trial was based on self-reported knee pain according to the NHANES-I criteria (Davis et al. 1992). Evidence of radiographic change was not employed as an entry criterion for this study since the principle interest was of symptomatic knee problems. Subsequent radiographs revealed that evidence of structural knee OA (≥ grade II) was present in 330 (47%) of subjects entering the trial.

Exclusion criteria for this stage of the study included the criteria previously outlined for the postal survey. In addition, volunteers were excluded upon telephone contact according to the following criteria:

- No knee pain in the last week.
- Total knee replacement.
- Lower limb amputees.
- Use of a cardiac pacemaker.

2.2.8 Materials and Procedures

2.2.8.1 Subject Recruitment

Initial contact was made by telephone to all potential volunteers (those subjects who had returned the postal survey with self-reported knee pain). Volunteers were asked if they had experienced pain within the last week in order to establish current knee pain status (this was done because of the inevitable delay between questionnaire completion and subsequent recruitment). If volunteers responded positively to this question, they were invited to attend at their local health centre for further assessment.

2.2.8.2 Assessment procedure

Assessments for consenting volunteers were conducted at their own GP surgery and took approximately one hour. Upon arrival, volunteers were given an information sheet to read and any unanswered questions were addressed. Signed consent was obtained. The initial assessment procedure included three sections as outlined in Table 10. A copy of the assessment questionnaire is appended (Appendix 3).

Table 10 Assessment procedure.

Self-completion questionnaires	• WOMAC (knee specific – pain, stiffness and physical function) • SF-36 (generic health status) • HAD (anxiety and depression) • EuroQol EQ-5D (generic utility measure of Quality-of-Life) • Cost data relating to the accessing of health provision, personal costs and work-related health difficulties
Physical assessment	• Height and weight • Knee examination - effusion, warmth, crepitus, bony swelling, joint line tenderness and range of movement • General examination - hands (Heberden's nodes, thumb IPJ nodes), hips (pain on rotation), back (pain on extension and flexion) • Hypermobility screen • Fibromyalgia screen
Muscle strength testing	• Isometric maximum voluntary contraction (MVC)

At the end of the initial assessment, volunteers were informed of the subsequent two-year intervention trial. A further information sheet was provided and questions addressed. Those volunteers agreeing to enter the trial were asked to sign a second consent form (this included informed consent to enrolment in the trial, and agreement for the researcher to access medical records as necessary). Volunteers were given an information leaflet about the trial and further information regarding the general management of knee pain (Appendix 4). Volunteers were instructed to continue all medications and other

treatments as prescribed by their existing health professional. In this way, treatment effects observed within the trial reflect incremental benefits over and above those achieved through existing care.

Follow-up assessments were conducted at 6, 12, 18 and 24 months. The 18-month assessment was a shortened version including only the WOMAC (primary outcome measure) and muscle strength testing. An additional short questionnaire was added at this assessment in order to assess patient satisfaction with the study treatments (Appendix 5). Those volunteers who dropped out of the study were contacted by post at 24 months and asked to complete a shortened version of the final assessment questionnaire (including: WOMAC, EuroQol EQ-5D and the short additional questionnaire). This procedure had two principle aims: i) to provide 24-month outcome data for all subjects, regardless of treatment adherence and ii) to more accurately determine any adverse effects resulting from participation in the trial.

2.2.8.3 Muscle strength assessment

Isometric muscle strength was assessed using a modified Tornvall chair (Jones, 1994; Tornvall, 1963). This technique was chosen as the most appropriate for the current study since measurement is relatively quick and simple to perform. Similar equipment has been successfully employed in both hospital and community settings, for patients both with and without knee pain (O'Reilly et al. 1998; Jones, 1994). The use of a Tornvall chair allows the accurate

positioning of each volunteer, with both hips and knees being flexed to 90°. Volunteers were strapped into the chair at the waist with extra cushioning provided to support the back. A strain gauge (± 50 KgF) TKA load cell (Techni Measure, Studley) was attached to the back of the chair and could be adjusted horizontally to allow for the measurement of both left and right legs. A strap was placed around the ankle of each volunteer and attached to the load cell via a portion of chain. The output from the gauge (± 2V) was connected to an amplifier and digital read-out (TML model TD-91M, Tokyo Sokki Kenkyujo Co. Ltd., Japan). The final output was read onto an Xyt chart recorder (BD92, Kipp and Zonen Delft BV, Netherlands) at practice A, and to a PC laptop at practice B.

Following explanation, volunteers were required to perform three voluntary contractions at maximum effort. If contractions were still increasing in strength at the third attempt (by at least 1 KgF), then volunteers were asked to perform a fourth pull. The highest reading obtained was used as the maximum voluntary contraction (MVC).

2.2.8.4 Radiographic assessment

All volunteers agreeing to enter the trial were asked to attend the Nottingham City Hospital Radiology department for radiographic assessment of their knees.

The following views were obtained:

- Standing weight-bearing antero-posterior radiograph of the tibiofemoral joint in full extension (Jacobsson, 1996).
- Skyline radiograph of the patellofemoral joint in 30° of flexion (Lanyon et al. 1996).

Of the 786 volunteers entering the trial, 706 (90%) attended for radiographic assessment. Radiographs were read by a single observer (Dr S.O.) and individual features were graded using a standardised atlas (Altman et al. 1995). For the purposes of this study, definite OA was defined by the presence of ≥ Grade I osteophyte in the tibiofemoral compartment and / or ≥ Grade II osteophyte in the patellofemoral compartment (with or without joint space narrowing).

2.2.9 Randomisation and blinding

Following assessment, volunteers were randomised in permuted blocks of ten into one of six treatment groups:

Group 1 (15%)	Home-based exercise + telephone support
Group 2 (15%)	Home-based exercise + telephone support + placebo
Group 3 (30%)	Home-based exercise
Group 4 (20%)	Telephone support
Group 5 (10%)	Placebo
Group 6 (10%)	Nothing

The nature of the interventions meant that it was not possible to blind participants to treatment allocation. Nevertheless, researchers responsible for conducting the assessments were blinded throughout the trial. For the purposes of randomisation, four computer-generated lists were employed (stratified by age and sex to include: males <65 years; males ≥65 years; females <65 years and females ≥ 65 years). Volunteers were preferentially allocated to the exercise groups, as pilot work suggested that drop out rates would be highest amongst these subjects (O'Reilly, 1996).

2.2.10 Exercise intervention

The exercise programme was designed to be simple to use, applicable for all age groups and readily assimilated into daily life. It consisted of flexibility exercises, unresisted and resisted strengthening exercises, functional exercises and aerobic exercises. The various exercises were introduced at different stages throughout the two-year programme with the primary aim of improving and maintaining quadriceps muscle strength over time (Table 11).

Table 11 Timetable for the exercise intervention.

Visit	Exercises Taught
Visit 1 (0 months)	Flexibility + unresisted strengthening exercises
Visit 2 (2 weeks)	Additional flexibility + unresisted strengthening exercises
Visit 3 (4 weeks)	Resisted exercises (trainer band)
Visit 4 (2 months)	Resisted (stronger band) + functional exercises
Visit 5 (7 months)	Selection of above (+ stronger band) + aerobic exercises
Visit 6 (13 months)	Review + stronger band if necessary
Visit 7 (19 months)	Review + stronger band if necessary.

The program was taught in volunteers' homes by a trained therapist. This was a pragmatic study and exercise visits were kept to a minimum. Such a design helped to provide more realistic costing data than would commonly be achieved through more intensive trials (van Baar et al. 1998b; Ettinger et al. 1997), whilst also reducing the potential for strong psychosocial input. A total of seven visits were undertaken throughout the two-year period as outlined in Table 11. It was recommended that exercises be carried out on a daily basis, and that they should take no more than 20-30 minutes to complete.

All volunteers were given an exercise diary containing written instructions on the individual exercises, general advice regarding exercise participation and a contact name and number (Appendix 6). The diary was also used to document treatment adherence throughout the period and was subsequently scored according to set criteria (see later section). New diaries were distributed every six months and old ones collected by the therapist.

Resisted exercises were taught using rubber exercise bands (Dynabands™ and Clinibands ™). The required band strength was assessed according to muscle strength readings taken during initial assessment. Stronger bands were issued at visits 5, 6 and 7, if subsequent strength gains were observed. Prior to exercising with a full-strength band, volunteers were left with a weaker, training band for 4-5 weeks in order to familiarise themselves with the exercise technique. (Table 12)

Table 12 Summary of exercise bands used according to MVC recordings.

MVC of weakest leg	Trainer band (Visit 3)	Band 1 (Visit 4)	Progression bands (Visits 5-7)
<10 KgF	Red	Red	Pink / Green
10.1-12 KgF	Red	Pink	Green / Blue
12.1-15 KgF	Red	Green	Blue / Red Doubled
15.1-18 KgF	Red	Blue	Black / Purple
18.1-21 KgF	Red	Black	Purple / Pink Doubled
21.1-30 KgF	Pink	Purple	Green Doubled
> 30 KgF	Green	Green Doubled	Blue Double / Grey

In order to establish the force generated by each of the bands, weights were attached to 1-metre lengths under laboratory conditions (Appendix 7). To achieve an increase in muscle strength during strength training, loads must be at least 60-70% of a person's maximum voluntary strength (Jones and Round, 1990). For the purposes of this study it was assumed that there would be an increase in band length of at least 100 cm, and that the force required in order to achieve this is represented in Equation 1.

Equation 1 Equation used to calculate the allocation of exercise bands by muscle strength.

MVC required = 60% (min. effort required) x 60% (adjustment for different positioning of leg during testing versus training) x MVC (measured during assessment).

2.2.10.1 Assessment of exercise adherence

Adherence with the exercise programme was assessed using the exercise diaries completed by study volunteers. Volunteers were instructed to record the type of exercise done and the number of repetitions for each leg on a daily basis.

Summary data for exercise adherence were produced according to set criteria (Appendix 8). The scoring scheme recognised:

- frequency of exercise completion (scored 1 – 5)
- number of repetitions per leg (scored 1 – 3)
- number of exercises completed per session (scored 1 –2)

This produced a score with a range of 1 to 8 (1 representing low adherence and 8 representing high adherence). Diaries were coded by therapists other than those responsible for teaching of the exercise programme, and were coded at a single time point for each 6-month period. In addition, 10% of all diaries were

re-coded by a second therapist and the resulting scores were compared for reproducibility.

Whilst volunteers were strongly urged to complete the exercise diary, full details were not always recorded. In this instance, the therapist was instructed to ascertain general exercise adherence at the follow-up visit and to record details of such in the diary as appropriate. The criteria used are listed in Table 13.

Table 13 Coding of exercise adherence if daily exercise diary was not completed.

Self-reported exercise frequency	Adherence code
Everyday or 5-6 days per week	7
3-4 days per week	4
1-2 days per week	2
None	1

2.2.11 Telephone support

Telephone support was primarily included in the study design as a control intervention for the psychosocial benefits of exercise participation. In this way, it has been possible to distinguish between a) the physical benefits of exercise therapy and b) the impact of regular patient contact. Nevertheless, social

support of this kind has been reported as producing clinically meaningful improvements in health status (Rene et al. 1992; Weinberger et al. 1986). Its importance as an independent treatment alternative has not therefore been ignored.

Treatment consisted of monthly telephone calls from a single researcher. The principle aim of calls was to monitor symptoms and to offer simple advice on the management of knee pain. For those volunteers receiving both telephone contact and exercise therapy, discussion of the exercise programme was discouraged and specific problems were referred back to the therapist responsible for teaching the programme. Health problems unrelated to the study were referred back to the volunteer's GP.

Calls were standardised in terms of content through the use of a simple checklist (Appendix 9). This checklist was not prescriptive however, and general social support was encouraged once rapport had been established. All calls were timed in order to facilitate economic evaluation of the trial.

2.2.12 Placebo intervention

In an attempt to encourage continued participation in the trial, half of the control group were allocated to receive a health-food product twice a week. This also allowed some examination of possible placebo effects operating within the trial.

Dolomite is a health food product containing calcium and magnesium. Although there are no clinical data, the producers of dolomite claim that it is beneficial for arthritis. Volunteers were required to take one tablet twice a week (considerably less than the recommended dose of 3 tablets per day). It has no known side effects.

2.2.13 No intervention control group

In order to control for participation in the trial, 10% of volunteers received no further intervention. These volunteers returned to the surgery for 6-monthly assessments, but had no other contact with the study team.

2.2.14 Scoring of health outcomes

Four well-validated instruments were employed during this intervention trial (Table 14). These are all self-completion questionnaires and were completed at the surgery during the 6-monthly assessments. The WOMAC osteoarthritis index (Bellamy, 1989) is a knee specific instrument (measuring knee pain, knee stiffness and knee-related physical function). The Likert (ordinal) version was used. The SF-36 (Garratt et al. 1993) is a generic health status instrument, the HADS (Zigmond and Snaith, 1983) is a generic measure of anxiety and depression, and the EuroQol EQ-5D (EuroQol Group., 1990) is a generic quality-of-life instrument. Table 14 outlines the domains used for each scale. Missing values were handled in accordance with the authors' guidelines.

Table 14 Summary of outcome measures used.

Instrument	Dimension	No. of items
WOMAC	• Pain	5
	• Stiffness	2
	• Physical function	17
SF-36	• Physical function	10
HADS	• Anxiety	7
	• Depression	7
EuroQol EQ-5D	• Mobility	1
	• Self care	1
	• Usual activities	1
	• Pain / discomfort	1
	• Anxiety / depression	1
	• Health utility	5

2.2.15 Outcome measures

2.2.15.1 Primary outcome measure

The primary outcome measure for this study was the WOMAC knee pain score achieved at 2 years. This involved 5 questions relating to the degree of pain experienced during daily activities such as walking, standing and sitting. Each question was scored on a 5-point Likert (ordinal) scale.

2.2.15.2 Secondary outcome measures

Secondary outcome measures included:

- Knee related stiffness and physical function – derived from the WOMAC (range 0-8 and 0-68 respectively).
- General physical function – derived from the SF-36 (range 0-100).
- Anxiety and depression – derived from the HADS (range 0-7 for both).
- Isometric muscle strength – measured in Newtons.
- Programme adherence – assessed through self-completion diaries (range 1-8).
- EuroQol – generic utility scale (range 0 – 1). Reported in Chapter 4.

2.3 Data management

2.3.1 General data management

All data were entered onto a customised database (Microsoft® Access 97), and analysis was conducted using SPSS for Windows version 8.0 (SPSS Inc., Chicago, IL). Data for the primary outcome measure (WOMAC scores at 24 months) were entered twice. Errors were amended as necessary prior to further analysis. For all remaining data, a 10% random sample was double entered. Accuracy in all instances was above 98%.

2.3.2 Handling of missing values

Where subjects failed to answer all necessary items, missing values were handled in accordance with the authors' guidelines for each instrument (i.e. the mean of the existing values was imputed for the missing value). For cases in which too many items were missing, values were carried forward from the previous assessment. This was not possible for baseline values and it was therefore necessary to exclude a small number of subjects from some scales. As a result, baseline group sizes vary for different outcome measures.

2.3.3 Intent-to-treat analysis

Between group comparisons were conducted on an intention-to-treat basis (Hollis and Campbell, 1999). This meant that data were analysed according to randomised groupings regardless of treatment adherence or study attrition. For subjects who dropped out, missed assessments or died during the period of the

study, values were carried forward from the last available assessment. Alternative means of dealing with uncertainty in the dataset were tested in sensitivity analysis and included i) the return of missing values to baseline scores and ii) the exclusion of subjects with incomplete data (per protocol analysis).

2.3.4 Number needed to treat

The number needed to treat (NNT) has been advocated as a clinically meaningful outcome for use in clinical trials (Cook and Sackett, 1995; Laupacis et al. 1988). Outcomes were presented as NNT figures in addition to change scores for knee pain at 24 months. For the purposes of this study, a clinically meaningful outcome was defined as being at least a 50% improvement in knee pain in a single individual. The number needed to treat is calculated by taking the inverse of the attributable risk, and confidence intervals are calculated by taking the inverse of confidence intervals for the attributable risk (Altman, 1998; Kahn and Sempos, 1989).

2.4 Statistical analysis

A significance level of 5% was employed throughout the study and confidence intervals were reported at the 95% level.

2.4.1 Primary outcome

Between group comparisons were based on change scores (baseline score was subtracted from the post-treatment score), rather than absolute values. This approach meant that variance within the dataset was minimised by adjusting for any (non-significant) baseline differences between the 6 treatment groups. A negative change score thus represented a post-treatment improvement in knee pain.

The primary outcome measure was the change in knee pain observed at 24 months. Between group comparisons (for the 6 treatment groups) were performed using one-way ANOVA. Individual p values were reported using Tukey's Honestly Significant Difference (THSD) and used the no intervention control group as the comparator. Factorial comparisons were performed using the independent samples t-test. Effect sizes were reported in addition to p values thus providing an indication of the degree of variance within the dataset (Matthews and Altman, 1996). Effect size calculations were performed using the following formula:

Equation 2 Effect size calculation

$$\frac{\Delta \text{ intervention group} - \Delta \text{ control group}}{\text{s.d. of } \Delta \text{ scores for whole population.}}$$

An effect size of 0.2 is generally considered to be small, 0.5 as medium and 0.8 as large (van Baar et al. 1998b).

The possible interaction of exercise and telephone support was explored using a factorial ANOVA model.

2.4.2 Secondary outcomes

Baseline characteristics were presented in a descriptive manner. Body mass index (BMI) was calculated using the following equation:

Equation 3 Calculation of body mass index

$$\text{Weight (kg)} / \text{height (m)}^2$$

All other secondary outcomes (WOMAC stiffness and physical function, SF-36 physical function, HADS anxiety and depression and voluntary muscle strength) were analysed by factor. Change from baseline was used throughout, and p values (independent samples t-tests) and effect sizes were calculated for each measure.

Muscle strength measurements (MVC) are reported in Newtons (KgF x 9.8). Analysis of muscle strength data presented methodological difficulties since the unit of measurement was that of the leg rather than the person. The difficulty of "two knees, one person" has been identified by others (Sutton et

al. 1997; Zhang et al. 1996). For the purposes of this study analysis was based on the left leg only.

2.4.3 Exploratory analysis

Further exploration of the factors associated with improved knee pain was conducted using multiple regression techniques. In order to combine data from each assessment period, a summary statistic based on the area under the curve (AUC) was calculated (Matthews et al. 1990). (Equation 4).

Equation 4 Area under the curve calculation for WOMAC pain scores.

((pain at 6 months – pain at baseline) / 2) + ((pain at12 months – pain at 6 months) / 2) + ((pain at 18 months – pain at 12 months) / 2) + ((pain at 24 months – pain at 18 months) / 2)

Exploratory analysis was based on per protocol data and included only those subjects with data for the entire period. Three models were developed; one for the entire study population, one for those subjects allocated to the exercise programme and one for those subjects not allocated to the exercise intervention.

Each regression model was developed in two stages. Variables were initially entered using a backward selection model (entry criteria of 10%). A second stepwise model was then conducted in which significant variables from the first

model were entered, plus factors of a-priori interest (treatment factor - exercise, telephone or dolomite and radiographic status). For the stepwise model, entry was set at the 5% level and exclusion at 10%. Assumptions were checked at each stage.

2.5 RESULTS

2.5.1 Postal questionnaire

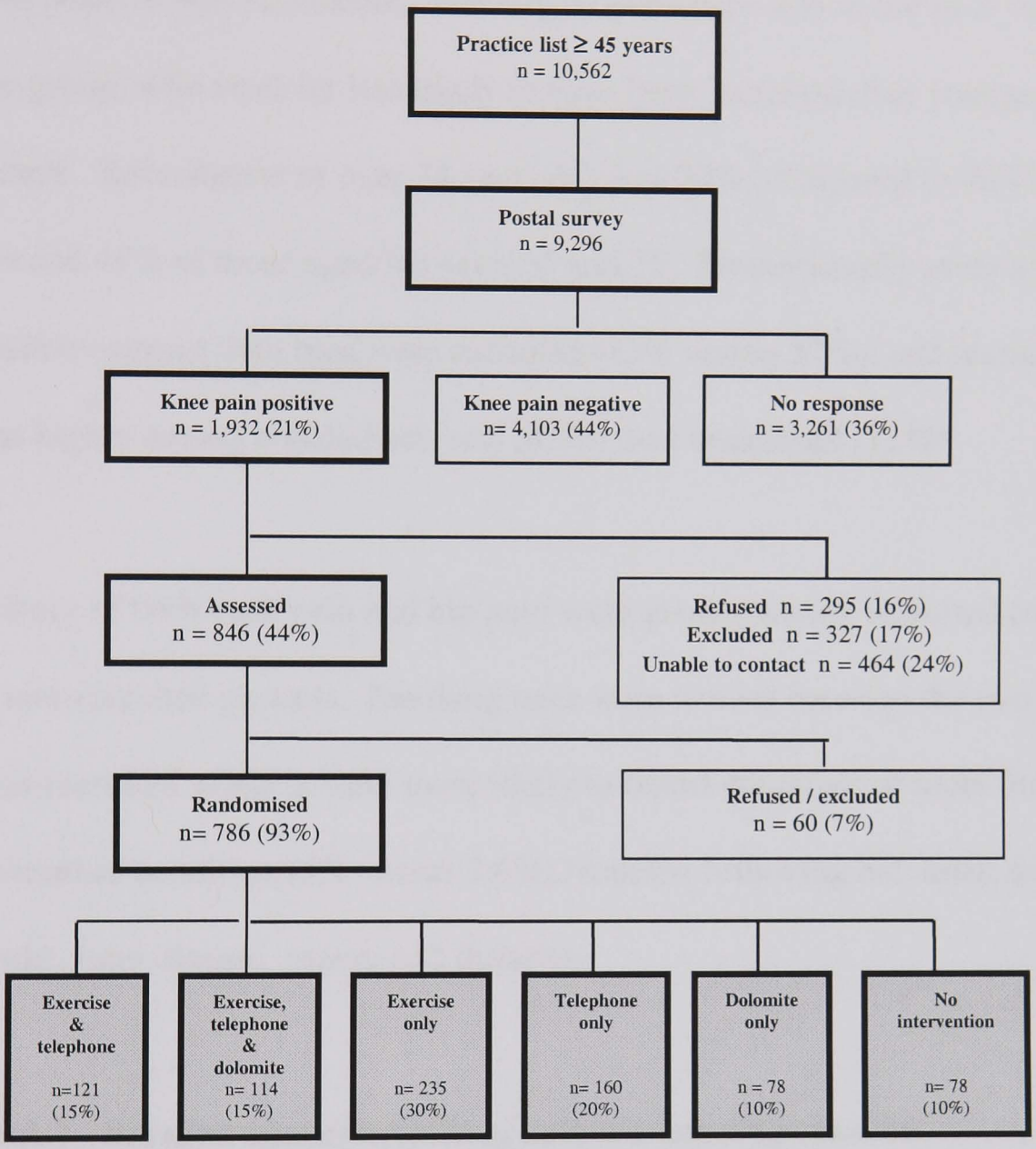
The postal survey was sent to 4541 patients from practice A and 4755 patients from practice B. Questionnaires were returned from 6035 individuals giving an overall return rate of 65%. Analysing the returned questionnaires, 1932 were from subjects who met the criteria for knee pain, giving an overall prevalence rate for knee pain in the community of 32% (21% of the total population). Gender-specific prevalence rates were 35% among females and 28% among males ($p = <0.01$).

All remaining data from the recruitment questionnaire has been used to inform a separate body of work and has not been reported in this thesis.

2.5.2 Recruitment for intervention study

Recruitment of volunteers for the intervention study took place from January 1996 to January 1997. Patient flow during recruitment is shown (Figure 9).

Figure 9 Summary of study recruitment.



2.5.2.1 Comparison of recruited and non-recruited subjects

The age distribution of study volunteers was different from that of the knee pain positive non-volunteers. The largest difference was in the over 75 years age group, who were far less likely to have been recruited than younger age groups. Recruitment of over 75 year olds was 20%, compared to 40% of under 55s and 48% of those aged between 55 and 75. Proportionally more knee pain positive women than men were recruited (43% versus 37%), and recruitment was higher among married subjects (45%) than unmarried (31%).

History of both back pain and hip pain were greater among recruited compared to non-recruited patients. Smoking rates were similar between the two groups. Non-recruited subjects were more likely to report diagnosis of more than one co-morbid condition (5% versus 2.6%) from the following list: heart disease, stroke, lung disease, cancer and diabetes.

2.5.2.2 Baseline characteristics of subjects entering the trial

Baseline characteristics of subjects entering the intervention trial are summarised (Table 15). In line with previous community studies, the majority (64%) were women, the average age was 62 years and 29% had a body mass index (BMI) of > 30 kg/m^2. Radiographic evidence of knee OA (≥ Grade II in either the tibiofemoral or the patellofemoral compartments) was present in 330 individuals (47%). Isolated patellofemoral OA was present in 58 (8.3%) of the study population and represents the number of cases that would have been

missed in prevalence studies based solely on radiographic evidence of tibiofemoral OA.

Table 15 Baseline characteristics of study population.

Patient characteristics	Total population n = 786	%	Non-completers n = 186	%	Significant difference
Practice A	317	40%	90	48%	#
Practice B	469	60%	96	52%	
Female	500	64%	126	68%	
Male	286	36%	60	32%	
Age:					#
45 to 54 years	189	24%	42	23%	
55 to 64 years	279	36%	55	30%	
65 to 74 years	243	31%	47	25%	
75+ years	75	10%	42	23%	
BMI					
Underweight <20 kg/m^2	8	1%	2	1%	
Normal 20 to 24.9 kg/m^2	188	24%	41	22%	
Overweight 25 to 29.9 kg/m^2	357	45%	86	46%	
Obese > 30 kg/m^2	231	29%	55	30%	
Radiographic changes	(n = 700)		(n = 143)		
< Grade II	370	53%	68	48%	
Grade II	330	47%	75	53%	
Comorbidity					
No comorbidity	615	78%	140	75%	
≥ 1 comorbid condition	171	22%	46	25%	
Baseline WOMAC pain					#
0 to 4	202	26%	34	18%	
5 to 7	212	27%	48	26%	
8 to 10	225	29%	61	33%	
11+	147	19%	43	23%	
Muscle strength (N)	n = 467		n = 95		
LMVC < 100	66	14%	19	20%	
LMVC 100 to 199.9	179	38%	35	37%	
LMVC 200 to 299.9	133	29%	24	25%	
LMVC >300	89	19%	17	18%	

Significant difference between non-completers and total study population. $\chi^2_{p=<0.01}$

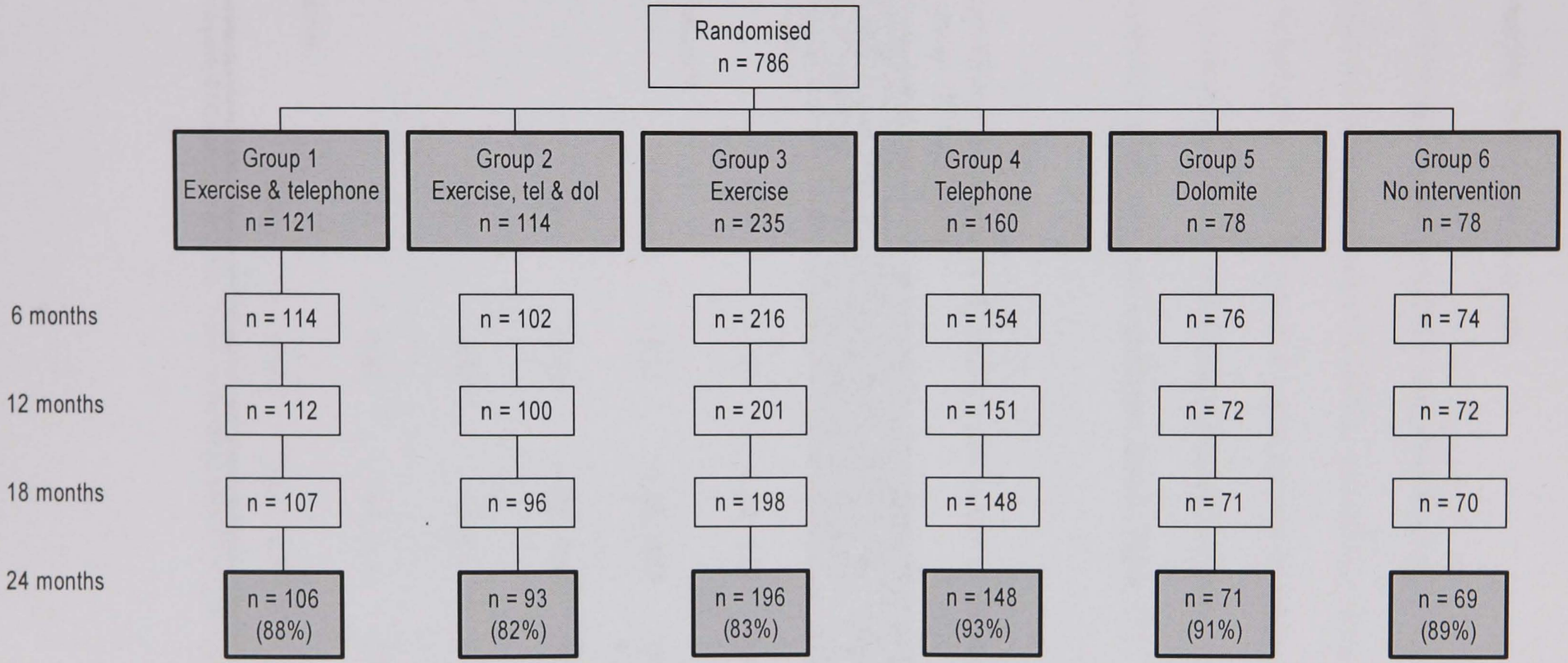
Randomisation was successful and no significant baseline differences were observed between the 6 treatment groups at baseline (Table 16).

Patient flow throughout the intervention study is shown (Figure 10). Study attrition was relatively low; 599 (76%) of volunteers completed the study and returned for final assessment at 24 months. Subjects who dropped out earlier in the study were contacted by post at 24 months and asked to complete a final assessment questionnaire. This resulted in the return of a further 83 questionnaires. Differences between completers and non-completers are tabulated (Table 15). Subjects who dropped out of the study were more likely to be aged > 75 years; have higher baseline pain scores; come from practice A; and be randomised to one of the exercise groups.

Table 16 Randomisation to treatment group (demographic details and key outcome measures).

	Exercise & telephone	**Exercise, telephone & dolomite**	**Exercise**	**Telephone**	**Dolomite**	**Nothing**
n	121	114	235	160	78	78
Age 45-54 years	26 (22%)	19 (17%)	66 (28%)	41 (26%)	20 (26%)	17 (22%)
Age 55-64 years	45 (37%)	48 (42%)	71 (30%)	56 (35%)	28 (36%)	31 (40%)
Age 65-74 years	37 (31%)	36 (32%)	78 (33%)	50 (31%)	20 (26%)	22 (28%)
Age ≥75 years	13 (11%)	11 (10%)	20 (9%)	13 (8%)	10 (13%)	8 (10%)
Female	74 (61%)	71 (62%)	150 (64%)	105 (66%)	49 (65%)	51 (65%)
BMI ≥30kg/m^2	36 (30%)	38 (33%)	69 (29%)	46 (28%)	20 (26%)	22 (28%)
Bilateral pain	89 (74%)	79 (69%)	161 (69%)	102 (64%)	50 (64%)	48 (62%)
Mean WOMAC pain	6.96	7.82	6.93	7.43	7.49	7.04
Muscle strength <100N	13 (18%) n = 74	11 (17%) n = 64	20 (14%) n = 141	10 (11%) n = 94	5 (11%) n = 45	7 (14%) n = 49
Structural change ≥grade 2	61 (54%) n=112	43 (43%) n=101	88 (42%) n=207	80 (57%) n=141	30 (42%) n=72	34 (57%) n=73

Figure 10 Progress of volunteers through the trial.



Subjects who dropped out during the trial were sent a final assessment questionnaire - this added a further 83 (11%) to the total at 24 months.

2.5.3 Primary outcome - self-reported knee pain at 24 months

2.5.3.1 Analysis by treatment group

A significant between group difference was observed in the change in WOMAC pain scores at 24 months (ANOVA, p = <0.01). This represented a significant reduction in pain for group 1 (exercise and telephone) compared to group 6 (no intervention). The remaining two exercise groups (groups 2 and 3) showed a similar, statistically non-significant trend (Table 17).

Table 17 Baseline and change in WOMAC pain scores at 24 months by treatment group (ITT analysis).

	Baseline pain	Mean Δ from baseline	95% C.I. for mean Δ	% Δ	Sig P*
Exercise & Telephone Group 1 (n=119)	6.96	-1.61	-2.22, -1.01	-23	0.02
Ex, Tel & Dolomite Group 2 (n=114)	7.82	-1.21	-1.86, -0.55	-15	0.19
Exercise Group 3 (n=234)	6.93	-1.13	-1.58, -0.69	-16	0.13
Telephone Group 4 (n=160)	7.43	-0.45	-1.0, 0.1	-6	0.96
Dolomite Group 5 (n=78)	7.49	-0.87	-1.55, -0.19	-12	0.67
No intervention Group 6 (n=78)	7.04	-0.06	-0.71, 0.59	-0.1	N/A

* Significance reported compared to group 6. Tukey's Honestly Significant Difference (THSD).

For comparison with previous studies, outcomes at 6 months are also shown (Table 18). The decrease in pain in the no intervention control group (group 6) meant that between group comparisons were non-significant, with the exception of the telephone support group (group 4), which showed a significant increase in pain.

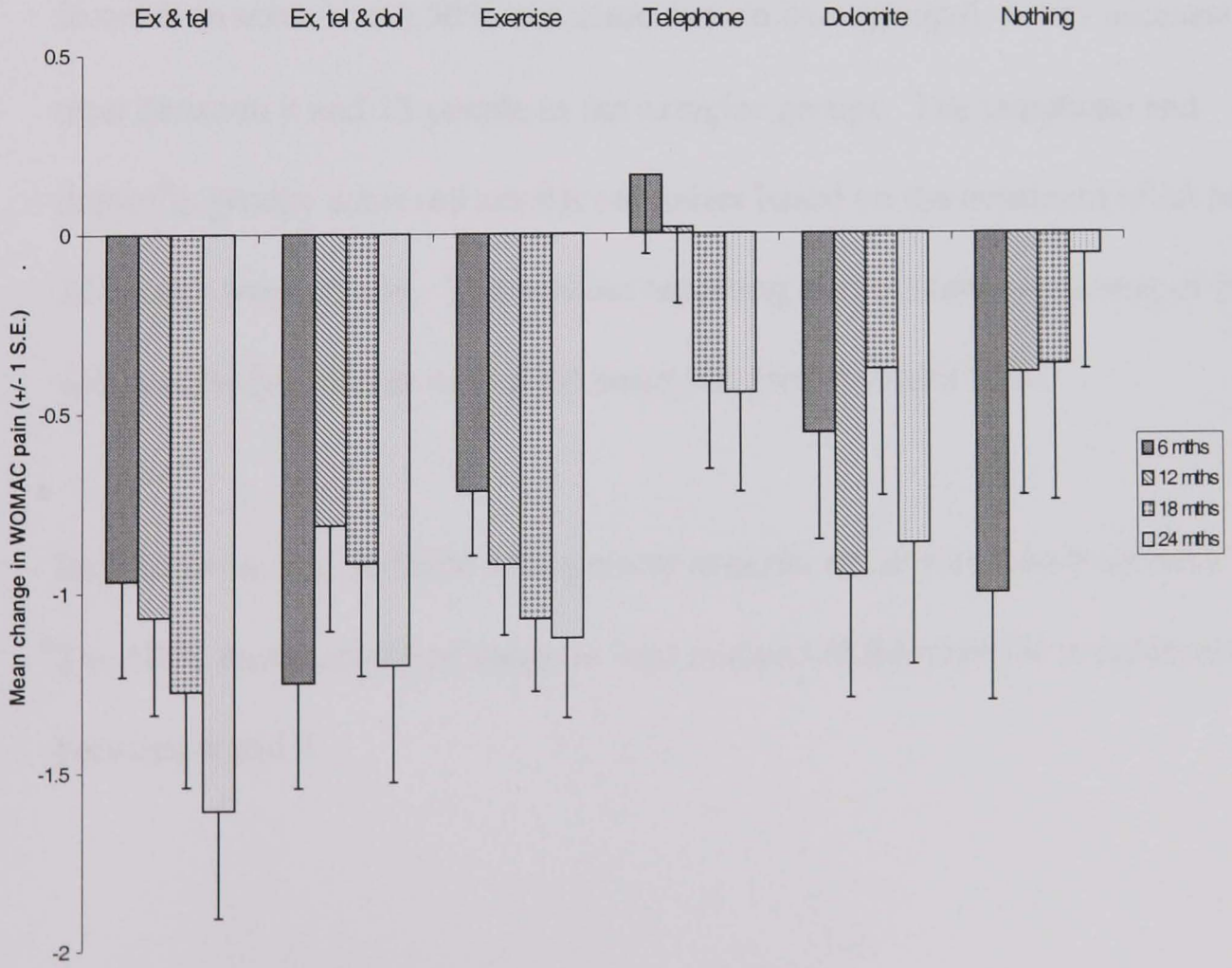
Table 18 Baseline and change in WOMAC pain scores at 6 months by treatment group (ITT analysis).

	Baseline pain	Mean Δ from baseline	95% C.I. for mean Δ	% Δ	Sig P*
Exercise & Telephone Group 1 (n=119)	6.96	-0.97	-1.50, -0.44	-14	1.00
Ex, Tel & Dolomite Group 2 (n=114)	7.82	-1.25	-1.84, -0.67	-16	0.99
Exercise Group 3 (n=234)	6.93	-0.72	-1.08, -0.37	-10	0.98
Telephone Group 4 (n=160)	7.43	0.16	-0.28, 0.60	2	0.03
Dolomite Group 5 (n=78)	7.49	-0.56	-1.16, 0.03	-13	0.92
No intervention Group 6 (n=78)	7.04	-1.01	-1.62, -0.41	-14	N/A

* Significance reported compared to group 6. Tukey's HSD.

Change in pain scores throughout the trial are shown graphically (Figure 11). The three exercise groups generally showed a consistent downward trend in reported knee pain throughout the period. Overall, the telephone group (group 4) showed the least improvement over time, with pain scores remaining relatively stable at all time points. The no intervention control group (group 6) showed a marked improvement at 6 months, although this effect had diminished to baseline levels by 24 months.

Figure 11 Mean change in WOMAC pain scores by treatment group (ITT analysis).



2.5.3.2 Number needed to treat

The mean reduction in pain for each of the exercise groups was approximately 1 to 1.5 points on the WOMAC pain scale. However, the clinical importance of such a finding is unclear. In order to address this issue, findings were presented on a "number needed to treat" (NNT) basis (Cook and Sackett, 1995; Laupacis et al. 1988). For the purposes of this analysis, a clinically significant improvement was defined as a reduction in pain of ≥ 50%. In producing the NNT statistic, each group was compared with the no intervention control group.

In order to achieve a ≥ 50% reduction in pain over group 6, it was necessary to treat between 8 and 13 people in the exercise groups. The telephone and dolomite groups achieved similar outcomes based on the treatment of 26 and 20 people respectively. The number reporting a significant worsening of pain was relatively constant across all treatment groups (Table 19).

Results presented in Table 19 represent analysis on an intent-to-treat basis. The NNT based solely on subjects who completed the exercise programme was between 6 and 8.

Table 19 Number needed to treat in order to achieve a ≥50% reduction in pain at 24 months (ITT analysis).

	Better by ≥50%	No change	Worse by ≥50%	Attributable risk	NNT (95% C.I.)
Ex & Tel Group 1 (n=121)	36 (30%)	74 (60%)	11 (9%)	0.13	7.7 (4.2, 11.2)
Ex, Tel & Dol Group 2 (n=114)	28 (25%)	73 (64%)	13 (11%)	0.08	12.7 (9.5, 15.9)
Exercise Group 3 (n=235)	65 (28%)	138 (58%)	32 (14%)	0.11	9.1 (5.8, 12.4)
Telephone Group 4 (n=160)	33 (21%)	102 (64%)	25 (16%)	0.04	25.5 (22.7, 28.3)
Dolomite Group 5 (n=78)	17 (22%)	52 (67%)	9 (12%)	0.05	19.6 (16.5, 22.7)
No intervention Group 6 (n=78)	13 (17%)	51 (65%)	14 (18%)	NA	NA

2.5.3.3 Analysis by factor

The number of treatment options within this trial meant that analysis of individual groups was limited by lack of power. Nevertheless, the factorial nature of the trial design allowed exploration of individual treatment factors. A highly significant difference was observed between exercise and non-exercise groups (Figure 12). Similar comparisons for the telephone and dolomite groups revealed no such differences (Table 20).

Figure 12 Mean change in WOMAC pain - exercise v non-exercise (ITT analysis)

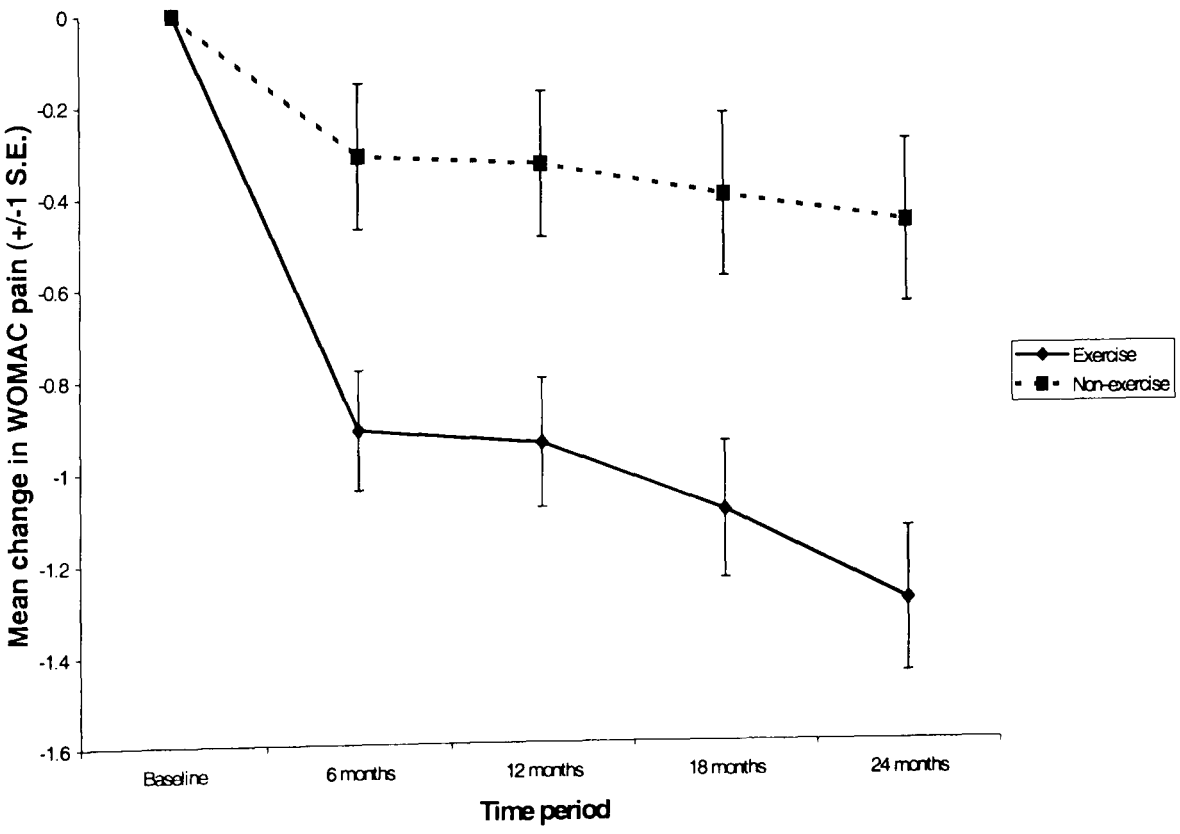


Table 20 Summary of WOMAC changes in pain scores by treatment factor at 24 months (ITT analysis)

	Baseline pain	Mean Δ from baseline	95% C.I. for mean Δ	% Δ	Sig. P*	Effect size
Exercise (n = 467)	7.15	-1.27	-1.59, -0.96	-18	0.001	0.25
Non-exercise (n = 316)	7.35	-0.46	-0.82, -0.1	-6		
Telephone (n = 393)	7.40	-1.02	-1.37, -0.68	-14	0.52	0.04
Non-telephone (n = 390)	7.06	-0.87	-1.19, -0.54	-12		
Dolomite (n = 192)	7.68	-1.07	-1.54, -0.60	-14	0.55	0.04
Non-dolomite (n = 591)	7.08	-0.92	-1.18, -0.63	-13		

* Independent samples t-test.

2.5.3.4 Interaction of factors

The possible interaction of exercise and telephone support was explored using a factorial ANOVA model. The addition of telephone support to the exercise programme did not result in significant improvement over the exercise only group (Table 21).

Table 21 Impact of the interaction of factors on WOMAC pain scores (ITT analysis).

	n	Baseline pain	Mean Δ 6 mths	Mean Δ 12 mths	Mean Δ 18 mths	Mean Δ 24 mths*
Exercise with Telephone	233	7.39	-1.11	-0.94	-1.10	-1.41
Exercise without Telephone	234	6.93	-0.72	-0.93	-1.08	-1.13

*Factorial ANOVA p = 0.54

2.5.3.5 Handling of missing values

Primary analysis has been conducted on an intent-to-treat basis. Analysis of this kind requires assumptions to be made in relation to missing data. Study attrition meant that data for WOMAC pain scores at 24 months were missing for 103 (13%) individuals. In order to explore the impact of these data on study conclusions, analysis was repeated using two alternative strategies.

i) Missing values imputed with baseline WOMAC pain scores.

ii) Per protocol analysis – complete data only.

In both cases, study conclusions were largely unaffected (Table 22).

Table 22 Alternative handling of missing data - WOMAC pain at 24 months.

	Baseline pain	Mean Δ	95% C.I. for mean Δ	% Δ	Sig. p*	Effect size
ITT ANALYSIS						
Exercise (n = 467)	7.15	-1.27	-1.59, -0.96	-18	0.001	0.25
Non-exercise (n = 316)	7.35	-0.46	-0.82, -0.1	-6		
RETURN TO BASELINE						
Exercise (n = 467)	7.15	-1.16	-1.46, -0.87	-16	0.002	0.22
Non-exercise (n = 316)	7.35	-0.45	-0.80, -1.07	-6		
PER PROTOCOL						
Exercise (n = 392)	6.99	-1.42	-1.77, -1.07	-20	0.001	0.27
Non-exercise (n = 288)	7.28	-0.5	-0.88, -0.12	-7		

* Independent samples t-test.

2.5.4 Secondary outcomes

A number of secondary outcomes were incorporated into the trial. For the sake of clarity, these have all been reported by factor rather than by treatment group.

2.5.4.1 Knee specific stiffness and physical function (WOMAC)

The two remaining domains of the WOMAC scale addressed the impact of the interventions on physical function and stiffness. The exercise groups showed a significant improvement in both of these domains over the non-exercise groups at 24 months (Table 23). No such improvements were observed for either the telephone or the dolomite groups.

Table 23 Change in WOMAC physical function and stiffness at 24 months – (ITT analysis).

	Baseline	Mean Δ	95% C.I. for mean Δ	% Δ	Sig. p*	Effect size
PHYSICAL FUNCTION						
Exercise (n = 466)	23.15	-2.59	-3.6, -1.6	-11	<0.001	0.25
Non-exercise (n = 316)	22.97	-0.02	-1.2, 1.1	-1		
Telephone (n = 394)	23.42	-1.43	-2.51, -0.35	-6	0.75	-0.02
Non-telephone (n = 388)	22.73	-1.63	-2.68, -0.68	-7		
Dolomite (n = 192)	24.16	-1.45	-3.0, 0.06	-6	0.88	-0.01
Non-dolomite (n = 590)	22.73	-1.59	-2.43, -0.74	-7		
STIFFNESS						
Exercise (n = 470)	3.42	-0.41	-0.6, -0.3	-12	0.01	0.18
Non-exercise (n = 316)	3.46	-0.13	-0.3, 0.04	-4		
Telephone (n = 395)	3.46	-0.27	-0.43, -0.12	-8	0.65	-0.04
Non-telephone (n = 391)	3.42	-0.33	-0.48, -0.17	-10		
Dolomite (n = 192)	3.66	-0.19	-0.40, 0.02	-5	0.28	-0.09
Non-dolomite (n = 594)	3.37	-0.33	-0.46, -0.21	-10		

* Independent samples t-test

Analysis at 6 months revealed similar results to those achieved at 24 months. Once again, no improvements were observed for either the telephone or the dolomite groups.

2.5.4.2 Muscle strength

Subjects in the exercise groups showed a significant increase in isometric muscle strength (MVC), compared to the non-exercise groups throughout the trial (Figure 13 – per protocol analysis; Table 24– ITT analysis). The greatest impact was observed at 6 months, when subjects allocated to the exercise intervention showed an increase in muscle strength of 5.3%. By contrast, those allocated to the non-exercise groups showed a reduction in muscle strength of 5.4%.

Figure 13 Change in muscle strength: per protocol analysis (practice B only).

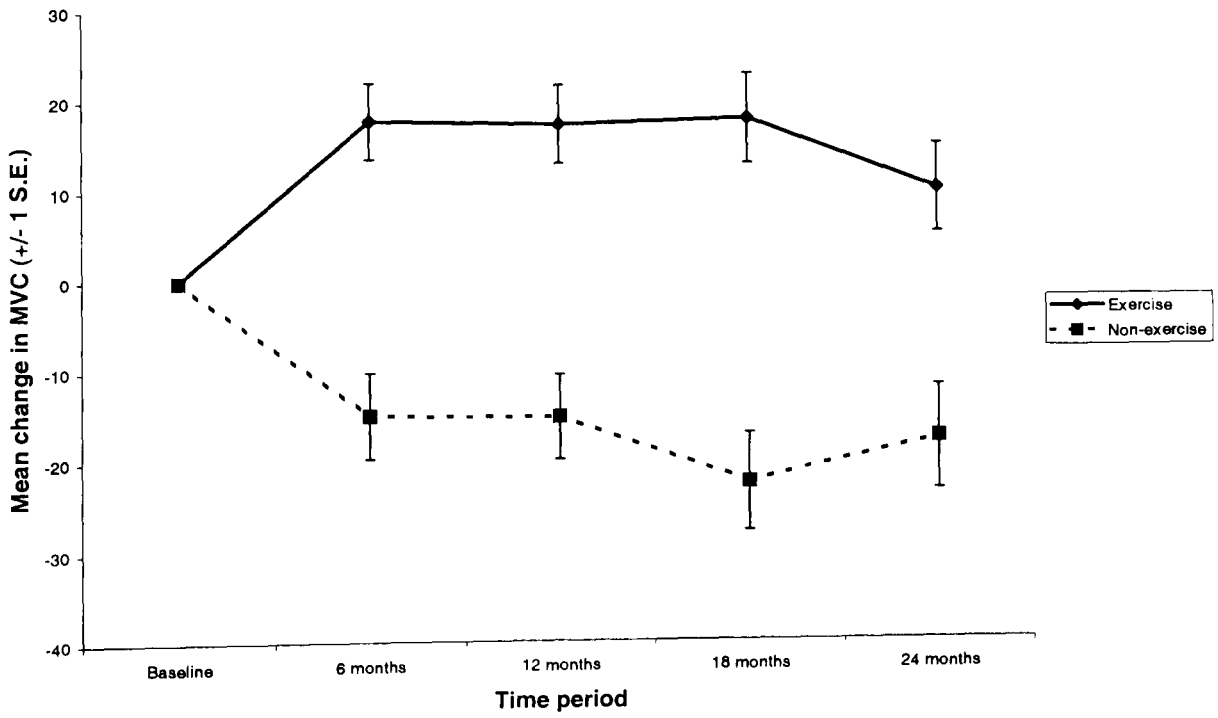


Table 24 Change in MVC at 24 and 6 months – practice B only (ITT analysis)

	Baseline MVC (Newtons)	Mean Δ	95% C.I. for mean Δ	% Δ	Sig. p*	Effect size
24 MONTHS						
Exercise (n=280)	212.2	4.8	-2.2, 11.9	2.3	<0.001	0.30
Non-exercise (n=189)	215.5	-13.6	-22.8, -4.3	-6.3		
6 MONTHS						
Exercise (n=280)	212.2	11.2	5.4, 17.0	5.3	<0.001	0.44
Non-exercise (n=189)	215.5	-11.6	-18.9, -4.2	-5.4		

* Independent samples t-test

Due to a calibration error during the recording of baseline MVCs for Practice A (n=317), all change scores were analysed based on data from Practice B alone (n = 469). Nevertheless, subjects were randomised to treatment groups in permuted blocks throughout the recruitment period. Any shift in calibration would therefore have affected all groups equally. As a result, it has been possible to repeat the analysis based on absolute scores for all subjects. Analysis in this way continued to show a significant effect (independent t-test; p = 0.02).

In order to explore the possible impact of a change in muscle strength on self-reported pain status, the data were examined by degree of change in muscle strength. Table 25 illustrates the significant difference in pain scores between those subjects who gained muscle strength and those who lost muscle strength.

This relationship showed a dose-response effect; the largest reductions in pain were seen amongst subjects with the greatest improvement in muscle strength.

Table 25 Impact of change in MVC scores on WOMAC pain scores at 24 months (all groups – practice B).

Δ MVC	Pain at baseline	Δ pain*	95% C.I. for mean Δ	% Δ	% Δ over control	Effect size
≥ 10% reduction (n = 160)	6.72	-0.19$^{\Psi}$	-0.7, 0.3	-2.8	-	-
No substantial change (n = 170)	6.80	-0.94	-1.4, 0.5	-13.8	-11	0.22
≥ 10% increase (n = 136)	7.29	-1.36	-2.0, -0.7	-18.7	-16	0.34

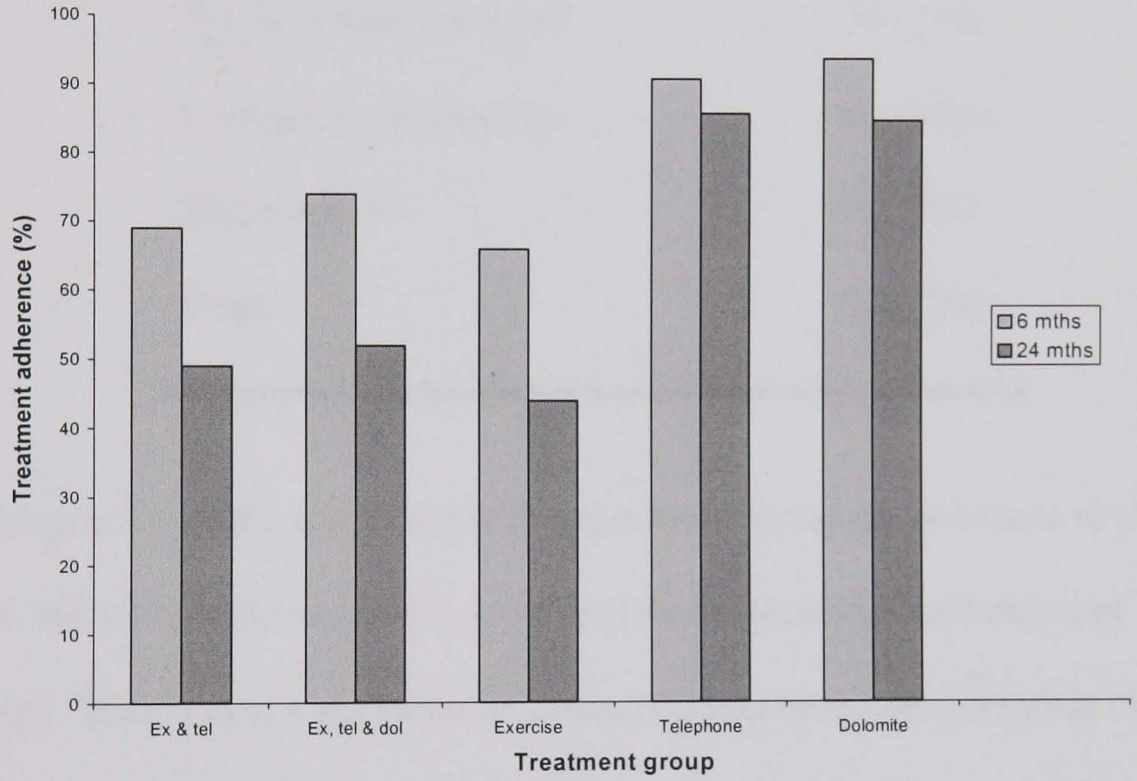
* One-way ANOVA, p = 0.01.

Ψ Used as comparison group for effect size calculation.

2.5.4.3 Exercise adherence

Treatment adherence decreased over the 2-year study period as shown diagrammatically (Figure 14).

Figure 14 Adherence with interventions at 6 and 24 months.



The most common reasons for non-completion of the exercise programme were related health problems involving back, hips and ankles (24%) and lack of time or motivation (23%) (Table 26).

Table 26 Summary of reasons for non-completion of the exercise programme.

Reason for non-completion	
Related health problems	57 (24%)
Lack of time / motivation	53 (23%)
Unrelated health / death	42 (18%)
Knees worse / no better	25 (11%)
Personal circumstances	24 (10%)
Knees better	6 (3%)
Other	28 (12%)

The degree to which adherence with the exercise programme relates to changes in WOMAC pain scores may help to explain the possible mechanism of change. Pain scores were examined by sub-group based on categories of low, medium and high adherence. Subjects who dropped out of the exercise programme prior to 24 months were included in the low adherence group; as were subjects who accepted treatment but failed to provide data relating to exercise activity (Table 27).

Table 27 Impact of exercise adherence on WOMAC pain scores at 24 months.

Adherence at 24 mths	Pain Baseline	Δ pain♦	95% C.I. for mean Δ	% Δ	% Δ over control (non-exercise#)	Effect size
Low n = 307	7.24	-1.01	-1.39, -0.62	-14%	-8	0.16
Medium n = 32	7.59	-1.63	-3.00, -0.25	-21%	-15	0.34
High n = 128	6.82	-1.83	-2.40, -1.26	-27%	-21	0.42

% Δ in WOMAC pain for non-exercise control group = - 6%.
♦ One-way ANOVA, p = 0.05

Two aspects are of particular relevance. Firstly, the number of subjects who maintained at least medium levels of exercise throughout the trial was 160 (34% of those randomised to the exercise programme). Secondly, a dose-response effect was observed. Greater reductions in pain were seen with increasing levels of exercise adherence. The effect size ranged from 0.16 for subjects in the low adherence group, to 0.42 for those in the high adherence group.

Of secondary interest was the impact of exercise adherence on subsequent changes in muscle strength. Both the medium and the high adherence groups showed a significant improvement in muscle strength over the low adherence group (based on data from Practice B only) (Table 28).

Table 28 Impact of exercise adherence on change in muscle strength (Newtons) at 24 months – practice B only.

	LMVC Baseline	Δ LMVC♦	95% C.I. for mean Δ	% Δ	% Δ over control (non exercise#)	Effect size
Low n = 173	213.1	-5.86	-14.2, 2.5	-2.8	3.5	0.12
Medium n = 15	226.2	25.31	-12.5, 63.1	11.2	17.5	0.62
High n = 92	208.4	21.61	8.8, 34.4	10.4	16.7	0.56

% Δ in LMVC for non-exercise control groups = -6.3%.
♦ One-way ANOVA, p = 0.01.

2.5.4.4 SF-36

A higher score on the SF-36 physical function score represents improved health status. This measure changed less than the WOMAC and although modest improvements were observed between exercise and non-exercise groups at 6 months, the effect was not sustained at 24 months (Table 29). No change was observed in either the telephone or the dolomite groups.

Table 29 Change in SF-36 physical function at 24 and 6 months (ITT analysis)

	Baseline PF	Mean Δ	95% C.I. for mean Δ	% Δ	Sig. p*	Effect size
24 MONTHS						
Exercise (n=457)	56.68	-0.65	-2.0, 0.8	-1	0.38	0.04
Non-exercise (n=309)	55.51	-1.62	-3.3, 0.04	-3		
6 MONTHS						
Exercise (n=457)	56.68	2.58	1.4, 3.8	4.6	0.05	0.08
Non-exercise (n=309)	55.51	0.74	-0.7, 2.2	1		

* Independent samples t-test

2.5.4.5 Anxiety and depression

Levels of anxiety or depression were not significantly altered by any of the study interventions. The mean scores for all subjects at baseline were 7.0 for anxiety and 4.7 for depression. For the purposes of screening, a level of >7 would indicate a potential clinical condition for each of these subscales (Zigmond and Snaith, 1983). In this population, 321 (41%) were rated as possibly anxious at baseline and 151 (19%) depressed. A summary of the results is presented (Table 30, Table 31).

Table 30 Mean baseline and change in anxiety scores by factor at 24 months (ITT data).

	Baseline anxiety	Mean Δ	95% C.I. for mean Δ	% Δ	Sig*. p
Exercise (n = 468)	6.91	-0.46	-0.7, -0.2	-6.7%	0.51
Non-exercise (n = 315)	7.11	-0.33	-0.6, -0.02	-4.6%	
Telephone (n = 393)	6.79	-0.30	-0.6, -0.03	-4.3%	0.23
Non-telephone (n = 390)	7.20	-0.53	-0.8, -0.3	-7.5%	
Dolomite (n = 191)	7.33	-0.58	-1.0, -0.2	-7.9%	0.31
Non-dolomite (n = 592)	6.89	-0.40	-0.6, -0.1	-5.8%	

* Independent samples t-test.

Table 31 Mean baseline and change in depression scores by factor at 24 months (ITT analysis).

	Baseline depression	Mean Δ from baseline	95% C.I. for mean Δ	% Δ	Sig*. p
Exercise (n = 468)	4.65	-0.05	-0.3, 0.2	-1.1%	0.5
Non-exercise (n =315)	4.74	-0.16	-0.4, 0.1	-3.4%	
Telephone (n = 393)	4.59	-0.02	-0.3, 0.2	-0.4%	0.4
Non-telephone (n = 390)	4.78	-0.18	-0.4, 0.05	-3.8%	
Dolomite (n = 191)	4.89	-0.02	-0.3, 0.2	-0.4%	0.3
Non-dolomite (n = 592)	4.62	-0.17	-0.4, 0.06	-3.7%	

* Independent samples t-test.

2.5.4.6 Patient satisfaction

Upon completion of the trial, participants were asked to complete a short questionnaire outlining their experience of participation in the study. A total of 641 (82%) questionnaires were returned (people who had previously dropped out of the study were invited to return the questionnaire by post).

The majority (62%) felt that they had benefited from participation in the trial. The most frequently reported benefit resulted from the study treatments themselves (228 responses), although improved knowledge and support was also an important factor (161 responses). More exercisers than non-exercisers reported personal benefit from participation (Table 32).

Adverse events resulting from participation in the study were reported by 95 (15%) subjects. Of these, 36 were related to events experienced during the 6-monthly assessments, 52 were related to the exercise programme and 7 were for miscellaneous reasons. Although largely minor (e.g. exercise band dug into ankle), the importance of exercise related adverse events should not be ignored and may be important in explaining poor treatment adherence.

Table 32 Self-reported beneficial and adverse events resulting from participation in the study.

	Exercise n = 371	Non-exercise n = 270	Total n = 641
BENEFIT			
Yes	257 (69%)	141 (52%)	398 (62%)
No	109 (29%)	128 (47%)	237 (37%)
Missing	5 (1%)	1 (<1%)	6 (1%)
ADVERSE EVENT			
Yes	73 (20%)	22 (8%)	95 (15%)
No	298 (80%)	247 (92%)	545 (85%)
Missing	0 (0%)	1 (<1%)	1 (<1%)

2.5.5 Multivariate analysis

WOMAC pain scores obtained at 6-monthly intervals were combined to produce a single dependent variable (AUC) for each subject. A negative AUC score represents a reduction in knee pain and therefore improved health outcome. This change score was examined for the possible effects of a number of independent factors including:

Baseline characteristics

Age, sex, BMI, radiographic status (≥ Grade II or normal), clinical signs (fibromyalgia, joint hypermobility, concurrent hip pain, concurrent back pain), self-reported comorbidity (absent or present), bilateral knee pain (absent or present), WOMAC knee pain scores, HADS anxiety and depression scores.

Factors relating to trial participation

Recruitment centre, intervention type, voluntary muscle strength at 24 months, change from baseline at 24 months for anxiety and depression.

Continuous variables were recoded as categorical variables in order to aid interpretation of results. Age, baseline knee pain and MVC at 24 months were entered based on quartile groupings. BMI was classified as underweight/normal, overweight or obese. Baseline anxiety and depression

were entered as binary variables reflecting the presence or absence of clinically meaningful cases (based on HAD scores of ≥7) (Zigmond and Snaith, 1983). Change in anxiety and depression were coded as being better than, the same as, or worse than baseline values. Full criteria for creating the model are outlined in the statistical methods section of this chapter (section 2.4.3). Entry into the final stepwise model was set at the 5% level and exclusion at 10%. Only actual data were used (not imputed values) and all necessary assumptions were met. Since muscle strength measurements were affected by the calibration error at practice A, baseline MVC and change in MVC scores were not included in the model. Nevertheless, it was possible to include actual MVC readings at 24 months as these were unaffected by the error.

Eight variables were found to be significant predictors of response ($R^2 = 27\%$, adjusted $R^2 = 26\%$) (Table 33). The most important of these were high baseline pain scores and low MVC readings at 24 months. Those with the worst pain at baseline showed the greatest improvement in knee pain, (although this may reflect regression to the mean). Individuals with low MVC scores at 24 months were less likely to report an improvement in pain. Even after adjusting for these variables, allocation to the exercise intervention remained a significant factor. In addition, radiographic OA, obesity, clinical anxiety at baseline, worsening anxiety during the period of the study and bilateral knee pain were all associated with poorer outcomes.

Table 33 Results of multivariate analysis for change in WOMAC scores throughout the 24-month period (dependent variable: Area Under the Curve)

	B coefficient	S.E.	C.I. for B	P	R^2
Baseline WOMAC pain >10	-11.7	1.06	-13.8, -9.6	<0.001	8.6%
MVC at 24 mths 0-140N	4.3	0.9	2.5, 6.1	<0.001	4.7%
Exercise	-2.8	0.7	-4.2, -1.5	<0.001	2.9%
Baseline WOMAC pain 7-9.9	-6.9	1.1	-8.9, -4.8	<0.001	2.9%
≥ Grade II OA	1.3	0.4	0.6, 2.0	<0.001	2.0%
Anxiety worse	2.9	0.7	1.5, 4.4	<0.001	1.5%
Baseline anxiety	2.5	0.7	1.0, 3.9	0.001	1.2%
Obesity	2.3	0.8	0.8, 3.8	0.003	1.2%
Baseline WOMAC pain 4-6.9	-3.1	1.0	-5.1, -1.2	0.002	1.2%
Bilateral knee pain	1.8	0.7	0.4, 3.2	0.01	0.8%

Residual s.d. = 0.99
Total R^2 = 27%

Two further models were constructed in order to assess the importance of each of these variables in explaining health outcomes for the exercise and non-exercise groups independently. For the 'exercise model', treatment adherence was included as an independent variable. In both models, results were broadly similar to those obtained for the whole population. However, the importance of structural change was no longer significant for the exercise group, whilst both structural change and self-reported back pain proved to be significant factors for the non-exercise group. Treatment adherence failed to reach significance in the exercise model; possibly due to its close association with muscle strength.

2.6 DISCUSSION

2.6.1 Main findings

This study demonstrates that exercise therapy can produce a moderate and significant reduction in self-reported knee pain amongst older, community dwelling adults over a 24-month period. Compared to the non-exercise control groups, exercise therapy resulted in an average reduction in knee pain of 12%. This effect was incremental to benefits resulting from normal care and is thus of considerable clinical relevance.

Improvements in pain were achieved by six months and sustained throughout the study period. Exercise therapy may therefore be considered a realistic treatment option, capable of providing long-term improvements in knee pain. Adherence with the programme was moderate. In those that adhered to the programme however, the exercises were well tolerated. The main reasons for non-adherence involved either related health problems (back, hips and ankles) or lack of time or motivation.

The number needed to treat statistic (NNT) provides a direct measure of the clinical importance of the findings. An improvement of ≥50% in reported knee pain was chosen as a clinically meaningful outcome in order to facilitate comparison with other studies. For example, a meta-analysis of the efficacy of topical NSAIDs suggested the NNT in order to achieve a ≥50% improvement in pain after 2 weeks of treatment was 3.1 (Moore et al. 1998). The NNT in the

current study was higher (mean = 10), but exercise therapy was delivered as an adjunct to normal care and outcomes were maintained over 2 years. Varying the trial period for outcome data can have a marked impact on efficacy findings. Two studies to examine the efficacy of intra-articular hyaluronic acid suggested that the NNT to achieve a ≥20% improvement in knee pain was 40.2 if outcomes were assessed at 1 year, whereas outcomes assessed at 35 days produced a NNT figure of 7.2 (Pendleton et al. 2000).

The introduction of telephone support and the placebo health food product contributed little to the observed improvements in knee pain. This finding supports the belief that exercise therapy can provide benefits beyond the potential psychosocial effects intrinsic to the delivery of the programme. The lack of an interaction between exercise and telephone in the two combined treatment groups also suggested that little could be added by the concurrent provision of social support. Nevertheless, the telephone intervention was specifically structured in order to avoid discussion of the exercise programme and may therefore have minimised any possible interaction. A more proactive intervention could potentially have resulted in improved exercise adherence (with its associated improvements in knee pain).

Results of the multivariate analysis supported the conclusion that exercise therapy was an important factor in the control of knee pain. Both allocation to an exercise group and muscle strength at 24 months were significant factors in the final model. Other modifiable factors included obesity and levels of

anxiety. Obesity has consistently been reported as a putative risk factor for knee OA (Felson et al. 1997; Felson, 1995; Cooper et al. 1994) and encouragement to reduce weight should ideally be included as a first line treatment (ACR subcommittee on osteoarthritis guidelines, 2000; Pendleton et al. 2000). The importance of anxiety in explaining self-reported knee pain points to the continued importance of psychosocial factors in pain management and may help to inform our understanding of the possible impact of educational support programmes.

The importance of concurrent back pain in the 'non-exercise model' may reflect the difficulty of developing condition specific outcome measures. Back pain has previously been identified as an important factor in determining WOMAC scores (pain, stiffness and physical function), along with other non-articular factors such as fatigue and depression (Wolfe, 1999).

2.6.2 Secondary outcomes

In addition to improvements in self-reported knee pain, the exercise programme produced significant improvements in knee stiffness and knee-specific physical function. These effects were relatively small, but again represented improvements beyond existing levels of care. More generic measures of health status (SF-36, HADS and EuroQol) did not show a significant effect. Given the nature of the trial interventions it was to be expected that knee-specific improvements might not have been reflected in

wider measures of quality-of-life. Other authors have reported similar limitations in using generic outcome measures (Fransen and Edmonds, 1999; Wolfe and Hawley, 1997; Bellamy, 1995). In particular, the presence of comorbidity could have exerted a dominant effect, which would have masked the limited knee-specific benefits (Xuan et al. 1999).

2.6.3 Comparison with other studies

This was a pragmatic study, the implications of which are important when seeking to make comparisons with other study findings. In general, it was anticipated that effect sizes achieved by the trial would be smaller than those reported in previous studies. Several factors contributed to this effect: i) analysis was on an intent-to-treat basis; ii) limited exclusion criteria were employed (resulting in high levels of comorbidity and relatively low baseline values for knee pain); iii) practical interventions were used, with limited input from health professionals; iv) effects were reported as incremental to normal care, and v) a relatively long-term period of follow-up was undertaken.

One study to have employed a similar design to that of the current trial was the Fitness Arthritis and Seniors Trial (FAST) (Ettinger et al. 1997). These investigators reported a 12% improvement in knee pain for subjects allocated to exercise therapy (compared to health education), which equates to an effect size of 0.5. Adherence with the exercise programme was roughly comparable to rates observed in the current trial. Outcomes were examined over an 18-

month period and analysis was conducted on an intent-to-treat basis. Treatment arms included exercise therapy (aerobic and quadriceps strengthening arms) and a health education control group. One difficulty with the trial was that health education was used as the control group. As a result it was not possible to quantify the health benefits of the education programme compared to no intervention. Interpretation of the incremental benefits of exercise therapy (compared to existing levels of care) was therefore difficult to establish. In addition, the exercise programme was delivered in a relatively intensive manner; involving a combination of both group therapy and individual home exercise. As such, it was intended as an exploratory trial to examine the benefits of exercise therapy in an optimal research environment.

Analysis of a less intensive home-based exercise programme was explored in a pragmatic study of 6-month duration (O'Reilly et al. 1999). This study randomised 191 adults aged 40-80 years with self-reported knee pain, to either home-based exercise or no intervention. The exercise programme was delivered as four home visits by the research therapist and consisted of quadriceps strengthening and aerobic exercises. At 6 months a 16% reduction in self-reported knee pain was reported for the exercise participants compared to the no intervention control group. However, the lack of a social support control group meant that it was not possible to quantify the psychosocial aspects of contact with the therapist.

An influential study to have examined the impact of aerobic exercise was a study by Kovar et al, (1992). This study examined 102 OA patients who were randomised to receive either supervised walking or no intervention. Outcomes were examined at 8 weeks and were thus of relatively short-term duration. The investigators reported an effect size of 0.6 for a reduction in knee pain. A recent follow-up to this study (Sullivan et al. 1998) examined outcomes at one year, post-treatment. It was found that continued adherence with the walking programme was low and that any significant improvements in pain status resulting from the intervention were subsequently lost. This reinforces the key importance of improving exercise adherence if benefits are to be sustained. The fact that the current study showed sustained improvements throughout the 24-month period of the trial suggests that the continued follow-up of patients at 6-monthly intervals may be an appropriate way to encourage continued participation.

A meta-analysis comparing patient education with NSAID use in both OA and RA patients (Superio-Cabuslay et al. 1996) was conducted in order to examine the incremental benefits of patient education. The average effect size for improvements arising from patient education was 0.17. However, there was a significant difference between education programmes that sought to affect behavioural change and those providing information and social support alone. This effect was also reported by Maisiak et al. (1996), who found that a combination of symptom monitoring and social support was less effective than a treatment aimed at increasing patient involvement and encouraging

behavioural change. The findings of the present study support this hypothesis in that the limited social support available through the telephone intervention was not sufficient to produce any improvement in health status.

2.6.4 Caveats

Every effort was made to reduce the methodological problems associated with some of the earlier trials into the efficacy of exercise therapy. Nevertheless, certain limitations need to be recognised. The trial sought to achieve both internal and external validity through its pragmatic design. However, the generalisability of the study findings was compromised by the significant differences between the pain positive subjects recruited into the trial and those not recruited. This means that extrapolation beyond the study population should be conducted with care.

Similarly, adherence was identified as being important in explaining the study findings. It is conceivable that adherence within the trial was higher than may be observed upon wider implementation. Subjects were aware that they were involved in a trial and that they would be contacted at regular intervals. The impact of a possible reduction in adherence should not therefore be dismissed.

Throughout the trial, primary analysis was based on intent-to-treat principles. Whilst this was intended to deal with missing data in as pessimistic a manner as possible, the technique does not avoid bias completely. It is possible that

short-term improvements seen at 6 months were simply carried forward to later time points for those subjects who dropped out of the study prior to 24 months. This could have artificially inflated improvements in pain at later assessments. However, sensitivity analysis (per protocol and return to baseline for missing values) suggested no such bias.

Blind assessment of treatment outcomes was a key feature of the trial design. Whilst every effort was made to ensure that this was maintained, the nature of the trial meant that this was not always possible. The regular contact between assessment metrologists and study volunteers meant that some degree of disclosure was inevitable. Nevertheless, the primary outcome was based on self-completion questionnaires and should not therefore have been influenced by any knowledge on the part of the research metrologist.

A more fundamental problem for the study was the fact that lack of power limited the ability to perform between-group analysis. Whilst factorial comparison of exercise and non-exercise groups was helpful, this limited the ability to distinguish between the various non-exercise interventions (telephone, dolomite and no intervention).

Finally, an important aspect of any exercise therapy is to establish that the programme does not aggravate existing symptoms. Evidence from the trial suggested a largely positive effect. However, it should be recognised that a dramatic worsening of knee pain may have resulted in premature drop out. As

a result, no evidence would have been gathered concerning these individuals. Nevertheless, complete data were available for 87% of subjects at 24 months and sensitivity analysis relating to the handling of missing data revealed no evidence of bias. Results of the patient satisfaction survey suggested possible adverse events in 20% of those subjects allocated to the exercise programme (compared to 8% for non-exercise participants). Whilst the majority of these events related to incidents of minor importance (e.g. the exercise band was uncomfortable around the ankle), their impact on possible treatment adherence should not be ignored. Evidence of radiographic progression of disease activity was not possible to assess in this study since subjects were not X-rayed at 24 months. The FAST study reported no evidence of change in radiographic status resulting from exercise therapy of this kind (Ettinger et al. 1997).

3 Cost of knee pain

3.1 Aims and objectives

Health costs incurred during the 6-month period prior to participation in the intervention study were assessed for all subjects. These data provided baseline values for the subsequent cost-effectiveness study and represented a period in time prior to contact with the study team. Two main objectives were addressed:

1. To explore the economic impact of knee pain in the community (including medical and personal costs).
2. To identify the factors most closely associated with high primary care costs.

3.2 Method

3.2.1 Study perspective

This cost-of-illness study reflects the costs incurred by study volunteers for the 6-month period prior to entry into the trial. A societal perspective was adopted, although the principle emphasis was on direct costs to the NHS. Comparison with a control group was not possible within the study design. As a result, the reported data are intended to provide an indication of the relative contribution of individual costs only.

3.2.2 Subjects

Subjects for the economic evaluation were taken from the intervention trial. They were categorised by diagnosis (OA or RA) on the a-priori assumption that the medical and personal costs incurred by RA subjects would be considerably higher than those incurred by OA subjects (Lanes et al. 1997). In the absence of a positive diagnosis of RA (or other connective tissue disorder) in the GP notes, subjects were classified as OA (regardless of radiographic status). RA patients were included in the economic analysis since the principle concern of the study was that of self-reported knee pain. Costs are reported both with and without these patients for comparative purposes.

3.2.3 Clarification of terminology

The terminology of economic evaluation lacks standardisation. In particular, disagreement over the appropriate use of several key terms has resulted in the same concepts being labelled differently by different authors (Pettiti, 1994). In order to avoid such confusion, a list of the key terms used in the following two chapters are documented in Table 34.

Table 34 Definition of key terms used in the current study and alternative definitions used by other authors (adapted from Petitti, 1994)

Term used by current study	Definition
Direct cost of treatment provision / intervention costs	*The cost of delivering the treatment under investigation (including labour and materials)*
Personal costs of treatment provision	*Costs incurred by patients as a result of the treatment under investigation.*
Medical costs	*Costs incurred by the health provider for normal treatment provision (including +ve and –ve consequences of direct treatment provision)*
Personal medical costs	*Costs incurred by patients in accessing normal health care provision.*
Indirect costs	*The cost of lost productivity due to ill health and / or treatment provision (including the concept of costs associated with alternative use of time).*
Additional costs / intangible costs	*The cost of pain and disability caused by knee pain.*

3.2.4 Costs included in the cost analysis

Having identified the major resource use implications of knee pain (adopting a societal perspective), the main cost drivers were chosen for further analysis. Items that were felt to be of minor importance, or were difficult to accurately quantify or cost, were documented in a qualitative manner.

Costs included in the final analysis were:

a) Medical costs – GP consultation costs, GP prescribed drugs and secondary care costs.

b) Personal medical costs – prescription charges, travel costs and OTC drugs.

Results are presented for primary care costs (GP costs + GP prescribed drug costs), total medical costs (primary care costs + secondary care costs) and societal costs (total medical costs + personal medical costs). The implications of excluding other costs from the main analysis were explored using sensitivity analysis.

3.2.5 Definition of costs

All costs are reported in pounds sterling at 1996 prices.

3.2.5.1 Medical costs

Details of service-use provision (GP costs, GP prescribed drug costs and secondary care costs) were obtained from an examination of patients' GP notes.

Obtaining frequency data from GP notes rather than through patient questionnaires has two main advantages:

- It reduces recall error. This may be particularly true of elderly, community dwelling adults with a chronic condition (Linet et al. 1989).
- It allows the collection of data for all subjects regardless of study attrition.

Details of related services (e.g. physiotherapy, chiropody and other primary care services) were recorded where possible, although reliable data were rarely available.

In an attempt to attribute resource use, data in all categories were recorded according to four criteria:

i) Exclusively related to knee pain.

ii) Partially related to knee pain:

   a) Only part of the consultation time involved talking about knees.

   b) Consultations involving the lower back, hips, ankles or feet.

iii) Side-effects of arthritis drugs e.g. gastrointestinal problems caused by NSAID use.

iv) Not related to knee pain.

3.2.5.1.1 *GP Costs*

These were based on frequency of GP consultations, treatments (injections or minor surgical operations), investigations (blood/urine tests, ECG recordings), radiographs and domiciliary visits. Unit costs were obtained from PSSRU (Netten and Dennett, 1996) and from the local hospital finance department.

3.2.5.1.2 *GP Prescribed Drugs*

Details of prescribed drugs were abstracted from GP notes and recorded according to the British National Formulary (BNF) classification scheme. The cost of individual drugs was based on average unit prices quoted in the September 1996 edition of the BNF. Drugs of particular relevance to arthritic conditions were identified by a consultant rheumatologist as outlined in Table 35, and were documented individually. Dispensing costs were excluded from analysis since it was unclear from previous studies whether they had been included or not. The impact of excluding such costs was explored in sensitivity analysis.

Table 35 Arthritis related drugs.

Drug Type		BNF Code
Oral NSAIDs	- normal - slow release	10.1.1
Topical NSAIDs		10.3.2
Analgesics		4.7.1 or 4.7.2
Gastro-intestinal drugs		1.3.1, 1.3.5 or 1.3.4
Other related drugs:		
• Steroids		10.1.2
• Tri-cyclic anti-depressants ≤ 50 mg		4.3.1
• Quinine (if quoted by patient)		10.2.2

It was not always possible to establish why particular drugs had been prescribed from GP case notes alone. Judgements were therefore based on retrospective data collected through patient questionnaires (Appendix 3).

3.2.5.1.3 *Secondary care costs*

Hospital costs were based on local figures from the finance department at Queen's Medical Centre, Nottingham. Outpatient and daycase costs were based on average rheumatology visits. Inpatient costs used the main cost drivers of number of days in hospital, and the number of days in intensive care. This was felt to best reflect actual resource use as figures produced for individual procedures by the hospital finance department did not take into account the often high levels of variance between individual patients. This was of particular relevance to the current study since arthritis is associated with high cost conditions such as obesity, diabetes and heart disease (Gabriel et al. 1999; Gabriel et al. 1997a).

The use of private medical facilities was documented separately. Total medical costs are reported both with and without these private costs. The personal cost of private health insurance was difficult to ascertain from questionnaire responses as monthly premiums were usually unknown or paid for by an employer.

Abstraction forms employed for case note abstraction are available in Appendix 10.

3.2.5.2 Personal medical costs

Three categories of costs were identified as relating to personal medical costs: a) prescription charges; b) over-the-counter (OTC) drugs and c) travel costs incurred whilst travelling to and from the health provider (GP surgery or hospital). Prescription and OTC drug costs were assessed using patient questionnaires (assessed retrospectively for the preceding 6 months). (Appendix 3). In order to avoid double counting of prescription costs (since they are a transfer payment), details have been documented in the personal costs section, but were not included in the total societal costs.

3.2.5.2.1 *Prescription charges*

Prescription charges were calculated at £5.50 per prescription issued. Exemption from prescription charges was assessed through the patient questionnaire. However, the relevant question was worded in the negative; *"Are you exempt from prescription charges?"*, and the resulting responses revealed clear confusion. As a result, prescription status was estimated for all periods based on a volunteer's age and employment status. All those under the age of 60 who were not registered as unemployed were assumed to pay prescription charges. Subjects who received more than 7 prescriptions in the 6 months prior to randomisation, were assumed to have purchased a prepayment certificate. As a result, a ceiling of £40 per person was imposed on prescription costs incurred during each 6-month period. It is hoped that the resulting data are a reflection of the actual personal costs incurred.

3.2.5.2.2 *Over-the-counter (OTC) drugs*

Items bought over-the-counter for the relief of knee pain were identified by subjects using the patient questionnaire. Drugs of interest were identified as being: NSAIDs, analgesics, rubs or gels and health food products (e.g. cod liver oil). Since much of the patient derived information was difficult to interpret, standard quantities (based on GP prescription data) were assumed for each identified purchase. Costs were based on prices quoted in the OTC directory 1995/6. (Table 36).

Table 36 Summary of quantity and price of OTC drugs.

Drug	Price based on	Quantity	Cost (6 months)
NSAIDs	Ibuprofen 200 mg	56 per month	£15
Analgesics	Paracetamol 500mg	50 per month	£18
Rubs / gels	Movelat 100g	One tube	£6.99
Health foods	Cod liver oil 500 mg	1 per day	£10

3.2.5.2.3 *Travel costs*

Cost incurred by patients for travel to and from the health provider (GP or hospital) were calculated based on average distances traveled. The staff travel rate for the local hospital of 37p per mile was used (mileage was estimated at two miles [74p] per doctor's visit and ten miles [£3.70p] per hospital visit).

Travel costs incurred by the friends and family of knee pain patients were not considered as part of this analysis.

3.2.5.3 Costs not included in the economic analysis

Details of other resource use were collected using patient questionnaires and included the following:

- Equipment purchased – an assessment of those items purchased by patients or outside agencies.
- Assistance from social services – provision of aids, meals-on-wheels, home-help.
- Eligibility for financial assistance – disability living allowance etc.
- Use of alternative health care – osteopathy, aromatherapy etc.

These data were not included in the formal economic analysis as the information related to services and equipment used for the relief of knee-related symptoms only (rather than total costs) and was collected over a different time period (12 months).

Medical costs relating to the professions allied to medicine (PAMs), such as physiotherapy, occupational therapy and chiropody were documented from GP notes. It has not been possible to provide accurate cost data for these professions since the number of sessions provided per treatment block was unclear.

Costs associated with lost productivity (indirect costs) were documented in a qualitative manner. The financial impact of excluding these costs was explored in sensitivity analysis.

Intangible costs (loss of leisure time, pain and disability) associated with knee pain were difficult to capture and cost in a meaningful way. Nevertheless, the need for informal care from family and friends was documented and provided some indication of the possible impact of knee pain on daily function. It was not felt appropriate to attach a monetary value to this care, and the need for help was documented in a descriptive manner only.

3.2.6 Unit costs

Unit cost and frequency of resource use are documented in Table 38 and Table 42 of the results section. Alternative costs may be applied as required

3.2.7 Data manipulation

3.2.7.1 General data management

All data were entered onto a customised database (Microsoft® Access 97), and analysis was conducted using SPSS for windows version 8.0 (SPSS Inc., Chicago, IL). Unit cost and total cost data are presented throughout; from which unit resource use can be calculated. It has been possible to calculate annual equivalent rates from the 6-month data, since recruitment was achieved

over a 12-month period. Any seasonal variation should therefore have been captured. The total costs and arithmetic mean are presented as being the most informative summary measures for policy decision-makers (Thompson and Barber, 2000; Barber and Thompson, 1998). Nevertheless, the median provides an indication of the degree of skew in the dataset and has been included for interest.

Primary care costs are reported in addition to total medical costs since the majority of knee pain sufferers are managed in the community. It was therefore of some interest to be able to isolate primary care costs.

The identification of costs specifically related to knee pain proved to be problematic. Attempts were made to classify all data as being either knee costs, partially knee related costs, costs resulting from NSAID related side effects, or unrelated costs. However, the specific joint of involvement or reason for a particular prescription were not always clear and it is possible that some degree of overlap or misclassification has occurred. Nevertheless, for the main analysis, total knee costs were defined as being:

Knee costs + 20% of partially knee related costs + 20% of NSAID-related side effect costs.

The decision to allocate 20% of the partially related costs and 20% of the side effect costs to the total cost of knee pain was taken after an examination of the

data capture forms and through discussion with consultant rheumatologists. Whilst it is hoped that this provides a best estimate as to the probable cost of knee related care, the probable impact of varying this percentage has been explored in sensitivity analysis.

3.2.7.2 Key assumptions

This cost-of-illness study is based solely on those items specifically outlined in earlier sections. It is not an exhaustive study of all possible cost implications. Rather, it is a pragmatic attempt to document some of the major cost drivers in relation to the medical management of knee pain in the community.

Whilst every effort was made to identify a broadly representative sample population, it should be recognised that all subjects were enrolled in the subsequent 2-year intervention programme. As a result, it is possible that generalisation of the observed health costs to a wider population may be problematic (Cronan et al. 1997b).

Finally, the majority of data collection was achieved through an examination of GP case notes. It is possible that unit resource use data have been underestimated as a result of inaccurate / inconsistent documentation or limitations in communication between primary and secondary care. It has not been possible to ascertain the degree of any such bias.

3.2.7.3 Regression analysis

Economic data provides a unique challenge for data analysis as it is usually highly skewed and frequently includes large numbers of patients who have incurred zero costs. In order to explore the data through regression analysis it was necessary to construct two-stages of analysis (Lipscomb et al. 1998):

i) Logistic regression model – to compare the characteristics of those patients who incurred costs with those who did not.

ii) Linear regression model – excluding those patients who incurred zero costs. This analysis assessed the factors most closely associated with high medical costs.

Secondary care costs were excluded from analysis since the predominance of low frequency, but high cost events would have reduced the predictive ability of the model.

The dependent variable for the logistic regression was defined by whether or not primary care costs were incurred during the six-month baseline period. Odds ratios (OR), confidence intervals (CI) and significance levels have been reported. The odds ratio (OR) is calculated as the exponential of the B-coefficient. An OR of greater than 1 represents increased risk, whilst an OR of less than 1 suggests a protective effect. Continuous variables were re-classified as categorical variables in order to aid interpretation.

Subjects who incurred no costs during the six-month baseline period were excluded from further analysis. Linear regression was then conducted using the log of the baseline primary care costs for the remaining subjects. Log transformation of the data was performed prior to inclusion in the model in order to meet the assumption of normality.

Both models were conducted in two stages. Variables were initially entered using a backward selection model (entry criteria of 10%). A second stepwise model was then conducted in which significant variables from the first model were entered, plus factors of a-priori interest (radiographic status and BMI). For the stepwise model, entry was set at the 5% level and exclusion at 10%.

3.3 Results

3.3.1 Subject characteristics

Subjects for the economic evaluation were taken from the intervention trial (n = 759). Case notes were unavailable for 27 subjects (patients had either died or left the surgery), and these subjects were excluded from further analysis. The demographic characteristics of the study population have been reported elsewhere (Table 15). Additional characteristics of relevance to the economic evaluation are summarised (Table 37).

Table 37 Summary of baseline patient characteristics.

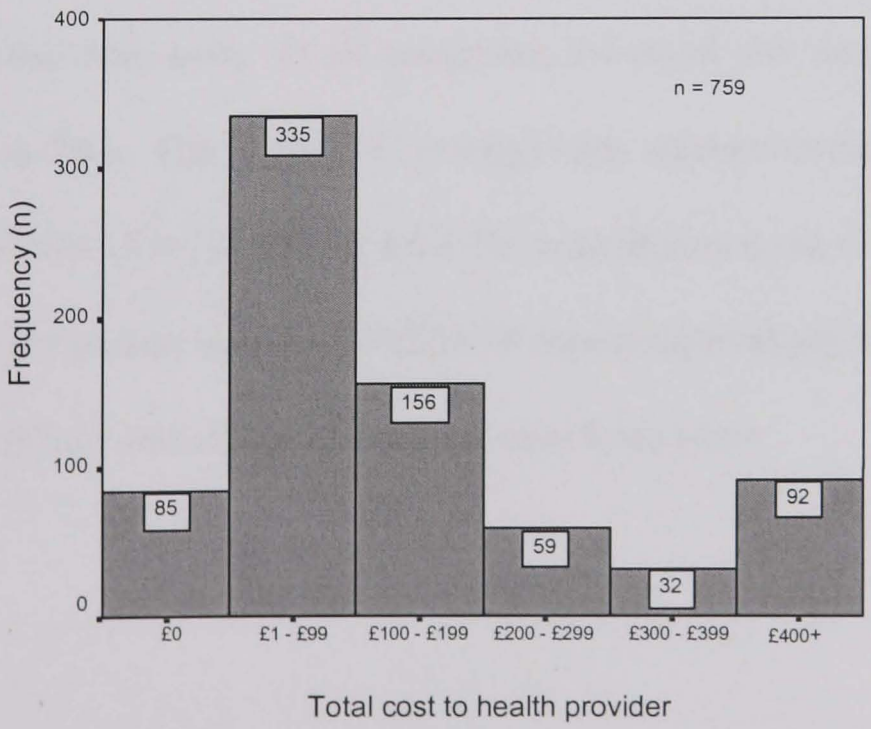
Patient characteristics	In study n (%)	Excluded n (%)
OA	729 (96)	27 (100)
RA	30 (4)	0 (0)
Prescription exempt	467 (61.5)	17 (63)
Private health insurance	88 (11)	2 (7)
Retired	440 (58)	16 (59)
Work full-time	139 (18)	4 (15)
Work part-time	100 (13)	3 (11)
Unemployed	49 (7)	3 (11)
Not employed	28 (4)	1 (4)

3.3.2 Medical costs

3.3.2.1 Total medical costs

The total medical costs incurred by the study population for the baseline 6-month period was £191,697 ($\bar{x}$ = £253). Costs were highly skewed with the majority of patients (55%) incurring costs of less than £100 (Figure 15). Of these, 85 (11% of total population) incurred no medical costs for this period. Of the 'high' service users (those who incurred costs of greater than £400), 36 incurred costs of over £1,000, with a range from £1,000 to £4,752 (with the exception of a single outlier of £25,366).

Figure 15 Total baseline costs to the health provider (6-month period).



The relative contribution of secondary care, GP prescribed drugs and GP consultation costs were £113,258 (59%); £56,906 (30%) and £21,533 (11%) respectively. Whilst secondary care costs represented the largest overall expenditure, this amount was incurred by 29% of the population and 69% of the total was accounted for by just 28 patients.

Total knee costs for secondary care, GP prescribed drugs and GP consultations were £5,285 (38%), £6,684 (48%) and £1,992 (14%) respectively. Knee related costs were consistently higher for patients with RA ($\bar{x}$ =£44.36) than for patients with OA ($\bar{x}$ = £17.33).

3.3.2.2 GP costs

GP consultation costs were relatively modest compared to secondary acre and GP prescribed drug costs. In all categories, the major cost driver was GP consultation time. The impact of investigations, treatments and radiographs contributed just 14% (£2,953) to total GP consultation costs (Table 38). The mean cost per person was £28.37 (£56.74 annual equivalent) for total GP costs and £2.63 (£5.25 annual equivalent) for total knee costs.

Table 38 Direct medical costs incurred during baseline 6 month period (knee costs = knee costs + 20% related costs + 20% side effect costs; totals rounded to nearest pound).

	Total cost (£) (n = 759)	**Total knee cost (£) (n = 759)**	**Knee cost excl. RA patients (£) (n = 729)**
GP COSTS			
Consultations @ £10	16,660	1,564	
Telephone contact @ £5	130	4	
Investigations / treatments @ £5	2310	160	
X-rays @ £9 per joint	513	144	
Domicilliary visits @ £30	1,920	120	
TOTAL	**21,533**	**1,992**	**1,779**
Mean (s.d.)	28.37 (30.6)	2.63 (8.5)	2.44 (8.4)
Median	20.00	0.00	0.00
ANNUAL EQUIVALENT	**43,066**	**3,984**	**3,558**
Mean (s.d)	56.74 (61.2)	5.25 (17.0)	4.88 (16.7)
HOSPITAL COSTS			
Inpatient 1st day @ £500	28,500	1,600	
Inpatient subsequent days @ £300	59,700	2,160	
Days in ICU @ £1,000	0	0	
Daycase surgery @ £480	5,280	96	
Outpatient new referral @ £100	7,100	520	
Outpatient follow-up @ £40	11,800	808	
A&E @ £42	798	101	
TOTAL	**113,258**	**5,285**	**5,041**
Mean (s.d.)	149.22 (976.9)	6.96 (91.0)	6.91 (92.9)
Median	0.00	0.00	0.00
ANNUAL EQUIVALENT	**226,516**	**10,570**	**10,082**
Mean (s.d)	298.44 (1,953.7)	13.93 (182.1)	13.83 (185.7)

Table 38 (Continued)

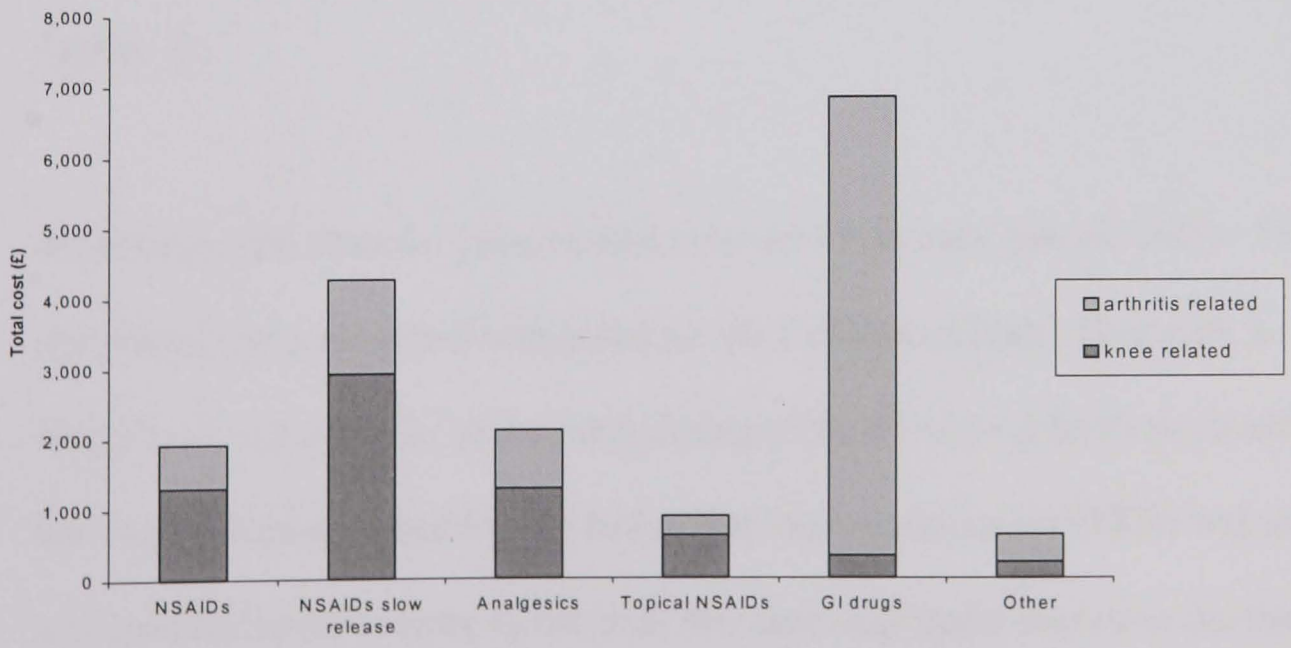
	Total cost (£)	Total Knee cost (£)	Knee cost excl. RA patients (£)
PRESCRIBED DRUGS			
ARTHRITIS DRUGS			
NSAIDs	6,218.74	4,240.47	
Topical rubs / gels	885.88	608.97	
Analgesics	2,126.09	1,290.16	
Gastrointestinal drugs	6,847.19	316.77	
Other arthritis related drugs	625.06	227.79	
TOTAL ARTHRITIS DRUGS	**16,703**	**6,684**	**5,810**
Mean (s.d.)	22.01 (50.2)	8.81 (23.5)	7.97 (21.1)
ANNUAL EQUIVALENT	**33,406**	**13,368**	**11,620**
Mean (s.d.)	44.02 (100.4)	17.62 (47.1)	15.95 (42.2)
TOTAL UNRELATED DRUGS	**40,203**	-	
Mean (s.d.)	52.97 (105.0)	-	
TOTAL DRUGS	**56,906**	-	
Mean (s.d.)	74.98 (123.9)	-	
ANNUAL EQUIVALENT	**113,812**	-	
Mean (s.d.)	149.97 (247.8)		
TOTAL PRESCRIPTIONS ISSUED (6 months)	**7,637**	**1,187**	**1,023**
Mean £ per prescription	7.45	5.63	5.68
TOTAL DIRECT MEDICAL COSTS	**191,697**	**13,961***	**12,630**
Mean (s.d.)	252.57 (1,023.7)	18.39 (94.7)	17.33 (95.8)
Median	80	0	0
ANNUAL EQUIVALENT	**383,394**	**27,922**	**25,260**
Mean (s.d.)	505.1 (2,047.4)	36.79 (189.4)	34.65 (191.6)
TOTAL PRIMARY CARE COSTS	**78,439**	**8,676***	**7,589**
Mean (s.d.)	103.35 (136.2)	11.43 (25.6)	10.41 (23.2)
Median	64.24	0	0
ANNUAL EQUIVALENT	**156,878**	**17,352**	**15,179**
Mean (s.d.)	206.70 (272.3)	22.86 (51.2)	20.82 (46.4)

* Total knee related costs represent 7% of total medical costs and 11% of primary care costs.

3.3.2.3 GP prescribed drugs

The cost of GP prescribed drugs was 2½ times the cost of GP consultations at £56,906. Arthritis related drugs contributed 29% to this total, with knee prescriptions alone being £6,684 (12%). The mean cost per person was £75 for all drugs, £22 for arthritis-related drugs and £9 for drugs taken specifically because of knee pain. Full details are tabulated (Table 38). On average, 10 prescriptions were issued per person ($\bar{x}$ cost per prescription to NHS £7.45), 1.6 of which were issued for knee pain ($\bar{x}$ cost per prescription £5.63). The relative contribution of each of the arthritis related drugs is shown (Figure 16). The importance of NSAIDs and gastrointestinal drugs to treat the side effects of NSAIDs in the treatment of arthritis is of particular note.

Figure 16 Contribution of drug type to total arthritis drug costs (6-month period).



The majority of prescriptions were issued to patients who were exempt from prescription charges. This meant that reimbursement through prescription charges contributed just 11% to the total cost (Table 39).

Table 39 Total drug costs in relation to prescription charges paid (6-month period).

	Drug cost to NHS (£)	Prescription charges paid (£)	% of total cost reimbursed
Knee related drugs	6,684	1,044	15.6%
Total drugs	56,906	6,128	10.8%

3.3.2.4 Secondary care costs

The impact of secondary care on total medical costs was high (59% of total cost). The majority of this amount was incurred as inpatient stays (£88,200). The mean cost per person was £149 (s.d. £977). Full details are tabulated (Table 38).

Secondary care costs for knee related care were relatively low (£5,285). Three operations (arthroscopies) accounted for 76% of this amount. However, a single knee replacement operation (costing £5,000) would effectively double the observed cost. Since having had a total knee replacement (TKR) was an exclusion criteria for entry to the trial, this data may under-represent the true cost of knee osteoarthritis.

3.3.3 Other medical costs

Details of professions allied to medicine (PAMs) were documented where possible (Table 40). Great variability existed in the quality of the data and figures should be used as a guide only.

Table 40 Number of PAMs sessions instigated through primary care (6-month period).

	Physiotherapy	Private physiotherapy	Chiropody	Psychiatrist	Dietician
Knee related	3	0	0	0	0
Partially knee related	9	4	2	0	0
Other	12	8	0	10	1
Total	24	12	2	10	1

In addition to physiotherapy provided in primary care, 4 courses of hospital-based physiotherapy were prescribed (1 for a knee complaint and 3 for back and hip complaints).

3.3.4 Personal costs

The personal costs incurred by patients in accessing medical care (prescription payments and travel costs) are summarised in (Table 41). The cost of items bought over-the-counter (OTC) has been documented separately since data for these items were collected for knee related purchases only (Table 42).

Table 41 Personal medical costs excluding OTC costs (6-month period)

n = 759		Prescriptions (exempt) n = 467	Prescriptions (non-exempt) n = 292	Travel – GP visits	Travel – Hospital visits	Mean (s.d)	Total
Knee costs	Units	848	339	156	31	-	-
	Units incurring cost #	0	217	N/A	N/A	-	-
	Cost	£0	£1,194	£116	£115	£1.88 (5.3)	£1,424
Total costs	Units	5,458	2,179	1,666	453	-	-
	Units incurring cost #	0	1,114	N/A	N/A	-	-
	Cost	£0	£6,128	£1,233	£1,676	£11.90 (16.0)	£9,037

Individuals who incurred more than 7 prescriptions within the 6-month period were assumed to have purchased a pre-payment certificate.

3.3.4.1 Prescription charges

Prescription charges reflect the costs incurred by 38.5% of subjects (the remainder being exempt from charges). Nevertheless, these charges contributed significantly to the total personal costs incurred. This was particularly so for total knee costs, where prescription charges accounted for 84% of the total personal costs and may reflect the importance of drug therapy for the treatment of OA.

3.3.4.2 Travel costs

Travel costs incurred by patients were generally low (£3.83 per person for total costs and £0.30 for knee costs). These figure represent direct travel costs and do not include an estimation of the opportunity cost of time spent travelling.

3.3.4.3 OTC drug costs

Drugs bought over-the-counter (OTC) represent a considerable cost to the individual. The cost of purchases made in this way was almost 3 times greater than the combined cost of travel and prescription charges (£3,996 : £1,424). The most frequently recorded purchases were for health food products (most commonly cod-liver oil), analgesics and topical preparations.

Table 42 OTC drugs bought for knee-related care (6-month period).

Drug type	Units	Cost (£)
Analgesics @ £15	89	1,602
Rubs / Gels @ £6.99	85	594
Health foods @£18	123	1,230
NSAIDs @ £15	38	570
Other @ N/K	6	N/K
TOTAL	**341**	**3,996**
Mean per person	**0.45**	**5.25**

3.3.5 Other costs

Other costs were collected retrospectively for a 12-month period. They refer to total knee costs only. Summary details are presented in Table 43.

Table 43 Other knee costs incurred over 12 months.

Support from social services n = 641	Number receiving support n (%)	Alternative health care	Number of sessions n
Adaptive aids	15 (2.3)	Osteopath / Chiropractor	7
Meals on wheels	2 (0.3)	Homeopathy / Aromatherapy	91
Home help	4 (0.6)	Toning tables	192

Social security payment n = 641	Number claiming allowance N (%)
Disability allowance	27 (4.2)
Mobility allowance	28 (4.4)
Attendance allowance	9 (2.0)
Carers allowance	6 (0.9)
Incapacity allowance	22 (3.4)
Other	5 (0.8)

3.3.6 Indirect costs

Of the 239 in paid employment, 18 (7.5%) reported having taken time off work due to knee pain. In total 303 days ($\bar{x}$ = 17 days) of sick leave were reported. The cost implications of time lost from work due to knee pain have been included in the sensitivity analysis.

In an attempt to capture the disease morbidity associated with knee pain, the need for informal care from friends and relatives was also documented (Table 44). Very few people paid for help with activities of daily living. Nevertheless, considerable need was identified, particularly in relation to

shopping, heavy domestic duties and bathing. Members of the immediate family generally provided assistance with these activities.

Table 44 The need for assistance with activities of daily living (due partly or fully to knee pain).

Type of activity n = 587	**Requires help**	**Receives help** (% of need met)	**Source of help** Live in	Live out	**Help paid**
Shopping	97	93 (96)	62	30	8
Cooking	14	14 (100)	10	4	2
Light domestic duties	12	11 (92)	9	2	2
Heavy domestic duties	178	143 (80)	93	46	19
Bathing	93	34 (37)	31	2	0
Showering	15	13 (87)	11	1	0
Dressing	29	21 (72)	21	0	0
Getting in / out of bed	14	11 (79)	8	1	1
Walking	45	21 (47)	13	3	3
Getting in / out of a car	72	52 (72)	21	26	0

3.3.7 Summary of total costs

Summaries of primary care costs, direct medical costs and societal costs for the study cohort are tabulated (Table 45).

Table 45 Summary of primary care costs, direct medical costs and societal costs (6-month and annual equivalent data, figures rounded to nearest whole pound).

	Total costs (£) n = 759	Knee costs (£) n = 759
PRIMARY CARE COSTS		
Total	78,439	8,676 (11%)*
Mean (s.d.)	103 (36.2)	11 (25.6)
Median	64	0
ANNUAL EQUIVALENT		
Total	156,878	17,352
Mean (s.d)	207 (272.3)	23 (51.2)
TOTAL MEDICAL COSTS		
Total	191,697	13,961 (7%)*
Mean (s.d.)	253 (1,023.7)	18 (94.7)
Median	80	0
ANNUAL EQUIVALENT		
Total	383,394	27,922
Mean (s.d)	505 (2,047.4)	37 (189.4)
SOCIETAL COSTS		
Total	198,602	18,187 (9%)*
Mean (s.d.)	262 (1027.3)	24 (96.5)
Median	98	10
ANNUAL EQUIVALENT		
Total	397,204	36,374
Mean (s.d)	523 (2,054.7)	48 (192.9)

* Figures in brackets represent knee costs as a % of the total cost for each category.
Estimated societal cost for UK population aged ≥45 years = £218 - £350 million (assuming prevalence of 21–35%).

3.3.8 Sensitivity analysis

Several assumptions underlie the economic analysis presented thus far. Their possible impact was explored through sensitivity analysis (Table 46).

Firstly, the impact of those variables excluded from the formal analysis should be noted. It was not possible to accurately document visits to the practice nurse. However, data obtained from GP notes suggested that between 20-50% of patients attended for a nurse visit during the study period. Data relating to services provided by PAMs (physiotherapy, chiropody, psychiatry and dietary advice) was equally limited. Nevertheless, the frequency data collected during the trial provides an indication of the possible cost implications. These figures should be treated with great caution as it was difficult to tell whether or not an entire course of treatment had been prescribed, or a 'one-off' consultation. Sensitivity analysis has been conducted assuming either extreme (i.e. each physiotherapy session was a single session versus a block of 15 sessions) (Netten and Dennett, 1996). Multi-way analysis including both nurse and PAM consultations suggested that total direct medical costs would be increased by between £1,487 (0.8%) and £6,522 (3.4%). The impact on knee costs was between £67 (0.5%) and £963 (6.9%).

For this analysis, local hospital unit costs were applied. Units of resource use were reported so that local values could be applied as necessary. However, it is interesting to note that national figures taken from the CIPFA 1995/96 database

suggest that total hospital costs could be up to 26% lower (£83,683) and knee costs 22% lower (£4,110). The majority of this discrepancy arose from differences in the cost of inpatient stays.

A total of 303 days were documented as being lost from work as a result of knee related illness. These costs were excluded from the main economic analysis but represent a substantial economic burden (based on GDP capita per head of £45 per day).(Moffett et al. 1999). The inclusion of indirect costs increased the societal cost of knee pain from £18,187 to £31,822 for the 6-month study period.

Dispensing costs were not included in the main analysis as it is unclear from previous studies whether such costs have been included or not. The impact of including dispensing costs is outlined (Table 46). Additional resource implications stem from the use of BNF prices for the costing of drugs. Prices quoted in the BNF do not accurately reflect the cost of drugs to the dispensing pharmacist. The Department of Health generally assumes that a discount of approximately 11% has been negotiated with the drug companies (personal communication). The combined effect of including dispensing costs, but discounting the total drug cost by 11%, resulted in little overall change in the estimated cost of prescribed drugs.

The possible impact of using subjects recruited into the subsequent RCT is more difficult to quantify. Other investigators have explored the cost

implications of studying elderly volunteers with osteoarthritis (Cronan et al. 1997b). These investigators found that non-volunteers were more likely to have a comorbid condition (particularly cancer), but that the overall number of health contacts for non-volunteers was lower than that for volunteers. However, the average cost of each contact was greater for the non-volunteer group. Overall, this resulted in roughly comparable total health costs between the two groups and further sensitivity analysis was not therefore felt to be necessary for the current data.

The identification of knee-specific costs was also problematic. For GP and hospital consultations it was not always clear if knee-related issues had been discussed. The previous analysis assumed that 20% of related costs (those for which knee pain formed only part of the consultation or in which other arthritis related locomotor conditions were involved) could be attributable to knee pain. This figure was based on an examination of the reason for service-use documented during data collection. Nevertheless, the figure was somewhat arbitrary and could have impacted on estimates of the overall knee costs. Results have therefore been presented assuming that 0 to 50% of the related costs were attributable to knee pain.

Finally, gastrointestinal drugs contributed 41% (£6,847) to the total cost of arthritis related drugs. This amount was almost entirely categorised as being unrelated to the knee pain, as only 3 individuals reported taking GI medicines as a result of their knee pain at a total cost of £317. It is conceivable that many

more patients were prescribed GI drugs as a result of GI complication stemming from the use of NSAIDs for the treatment of knee pain and knee drug costs may therefore be underestimated. Sensitivity analysis assessed the impact of re-categorising up to 50% of GI drugs as knee-related drug costs. Multi-way analysis exploring the possible impact of both of these issues suggests that direct medical costs for the knee could be reduced by £1,645 or increased by £6,349.

Table 46 Sensitivity analysis (figures in brackets represent change in costs).

	Total cost		Knee cost	
	Min.	**Max.**	**Min.**	**Max.**
Inclusion of nurse visits @ £6	**20% attended**	**50% attended**	**N/A**	**N/A**
Total direct medical cost	192,608 (+911)	193,974 (+2,277)	-	-
Inclusion of PAMs	**Per session**	**Per block**	**Per session**	**Per block**
Total direct medical costs	192,273 (+576)	195,942 (+4,245)	14,028 (+67)	14,924 (+963)
Multi-way analysis (Nurse + PAMS)	**193,184 (+1,487)**	**198,219 (+6,522)**	**14,028 (+67)**	**14,924 (+963)**
Definition of knee costs (% of related costs included)	**N/A**	**N/A**	**0%**	**50%**
Total direct medical costs	-	-	12,316 (-1,645)	16,429 (+2,468)
Definition of knee costs (% of GI drugs included)	**N/A**	**N/A**	**20%**	**50%**
Total direct medical costs	-	-	13,961 (+0)	17,842 (+3,881)
Multi-way analysis (definition of knee costs)	**N/A**	**N/A**	**12,316 (-1,645)**	**20,310 (+6,349)**
Dispensing costs included	**£0.00**	**£0.90**	**£0.00**	**£0.90**
Total direct medical costs	191,697 (+0)	198,570 (+6,873)	13,961 (+0)	15,029 (+1,068)
Drug tariff discount applied	**-11%**	**0%**	**-11%**	**0%**
Total direct medical costs	185,437 (-6,260)	191,697 (+0)	13,226 (-735)	13,961 (+0)
Multi-way analysis (drug costs)	**185,437 (-6,260)**	**198,570 (+6,873)**	**13,226 (-735)**	**15,029 (+1,068)**
Inclusion of indirect costs @£45 per day.	**N/A**	**303 days**	**N/A**	**303 days**
Societal costs	-	212,237 (+13,635)	-	31,822 (+13,635)

3.3.9 Regression analysis

Total primary care costs were included as the dependent variable in a two-stage model exploring the possible impact of a range of independent variables.

Factors included in the model were as follows:

Demographic characteristics:

Age, sex, BMI and recruiting practice.

Health status measures

Clinical diagnosis (OA/RA), self-reported comorbidity (comorbidity absent or present), clinical signs [fibromyalgia, bilateral knee pain, concurrent hip pain, concurrent back pain (absent or present)], WOMAC knee pain, radiographic status (≥ Grade II or normal), anxiety and depression.

Age, BMI, knee pain scores, anxiety and depression were entered as categorical variables in order to aid interpretation. Age and knee pain were entered based on quartile groupings. BMI was classified as underweight/normal, overweight or obese. Anxiety and depression were entered as binary variables reflecting the presence or absence of clinically meaningful cases (based on HAD scores of ≥7) (Zigmond and Snaith, 1983). In all cases, the reference group was that which would be expected to incur the lowest costs. Sufficient numbers (>100

cases) were available for each of the groups. It was not possible to include muscle strength scores in the final model because data relating to subjects recruited from practice A were subject to a calibration error during the collection of baseline readings.

Full criteria for developing the models are outlined in the statistical methods section of this chapter. Two models were fitted, firstly a logistic regression analysis. This compared the characteristics of individuals who incurred primary care costs (n = 674) with those who did not (n = 85). Individuals who incurred primary care costs were then entered into a further linear regression model, which identified the factors most closely associated with high primary care costs. In order to adjust for the highly skewed distribution of the dataset, log transformation of the data was performed prior to inclusion in this model. All necessary assumptions were then met.

3.3.9.1 Logistic regression

The final logistic regression model included 672 cases (87 were excluded due to missing data). Three variables were found to be significant risk factors for incurring primary care costs: comorbidity (OR = 12.7), WOMAC pain scores of ≥10 (OR = 3.2) and HADS anxiety scores of ≥7 (OR = 2.3). Full details are tabulated (Table 47). BMI and radiographic status were not included in the final model (p = 0.4 and p = 0.3 respectively).

Table 47 Results of logistic regression – risk factors for incurring primary care costs.

	OR	95% C.I	Sig. (p)
Comorbidity	12.67	3.1, 52.5	<0.001
WOMAC pain ≥10	3.18	1.3, 7.4	0.007
Clincally relevant anxiety (HAD ≥7)	2.26	1.3, 4.0	0.005

3.3.9.2 Linear regression

In the linear regression model seven variables showed an association with primary care costs (R^2 = 20%, adjusted R^2 = 19%). The most important factors were a) WOMAC pain score of greater than or equal to 10; b) at least one comorbid condition; c) self-reported back pain and d) clinically relevant depression. All factors demonstrated a positive relationship.

Knee pain was an important factor in dictating primary care costs. By contrast, radiographic evidence of structural change and BMI were not included in the final model (p = 0.5 and p = 0.3 respectively). Nevertheless, it is possible that structural change may better predict secondary care costs (particularly the need for invasive procedures such as arthroscopy or knee replacement surgery).

Table 48 Results of linear regression – primary care costs (6-month period)

	B coefficient	S.E.	95% C.I. for B	P	R^2
WOMAC pain ≥10	0.42	0.08	0.26, 0.59	<0.001	7.1%
Comorbidity	0.51	0.08	0.36, 0.67	<0.001	6.0%
Back pain	0.22	0.07	0.08, 0.35	0.002	2.2%
Clinical depression (HAD ≥7)	0.28	0.09	0.11, 0.45	0.002	1.6%
R/A	0.41	0.16	0.11, 0.72	0.01	1.1 %
Practice B	0.16	0.07	0.03, 0.30	0.02	0.8%
WOMAC pain 7 - 9.9	0.19	0.09	0.03, 0.36	0.02	0.7%
Female	0.15	0.07	-0.29, -0.01	0.03	0.7%

Residual s.d. = 1.01

Total R^2 for model = 20.3%

3.4 Discussion

3.4.1 Main findings

The cost of knee pain has been assessed in this cost-of-illness study. It provides UK data in relation to both the total costs incurred by patients with knee pain and knee-specific costs. This study is unique in that previous data have come largely from the USA and have looked at the cost of arthritis in general. Knee costs were found to be modest ($\bar{x}$ = £37 per annum for health service costs, $\bar{x}$ = £48 for societal costs). Knee costs represented approximately 10% of the total medical costs in the study sample. As is common with cost data, results were highly skewed and a small percentage of the population incurred extremely high costs. One individual incurred costs of over £25,000 for the 6-month study period. Nevertheless, a large number of those examined incurred no cost at all. Despite the relatively modest knee costs, the high prevalence of knee pain in the community ensures a substantial economic burden. Assuming a prevalence rate of between 21% and 32% for this population, the estimated total cost of knee pain in the UK for people aged 45 years and over at 1996 prices would be between £218 million and £350 million (excluding indirect costs).

The importance of secondary care and prescribed drug costs in dictating health-related costs for OA has been reported elsewhere (Lanes et al. 1997). The current study confirmed the importance of these aspects of care. In this population, drug costs were substantial, and were incurred by almost all

individuals (84%). By contrast, secondary care costs were incurred by few (29%), but were generally at very high cost.

Of the prescribed drugs identified, slow release NSAIDs and GI drugs were commonly prescribed. These were very expensive; the total cost of these two categories alone accounted for 78% of the total arthritis related drugs bill. Recent guidelines recommend the first-line treatment for the management of knee OA as being simple analgesics e.g. paracetamol and topical preparations, coupled with simple advice on weight loss and exercise therapy (ACR subcommittee on osteoarthritis guidelines, 2000; Pendleton et al. 2000). NSAIDs are reserved as second-line treatments because of their known association with GI complications, particularly amongst elderly patients. It is also of note that very few of the study population received formal physiotherapy for their knee pain or advice on exercise therapy. However, it is possible that simple advice by the GP may have been given but not recorded in the GP notes.

Personal costs included in the study were relatively high, particularly for the purchase of OTC preparations; most notably health food products. As is common with many chronic conditions, alternative means of coping with the condition are an important source of perceived patient need (Woolf and Doherty, 2000).

Given that the majority of those recruited to the study were either retired or unemployed, it was anticipated that the indirect cost of lost productivity would be relatively modest. However, indirect costs were considerable (£13,635) and increased the estimated knee related costs by 70%. The importance of indirect costs for individuals with osteoarthritis has been identified previously (Gabriel et al. 1997b; Gabriel et al. 1995; Badley, 1995b).

Finally, the intangible costs associated with knee pain should not be ignored. Considerable disability and the need for informal care were identified. These aspects of the condition are extremely difficult to cost in a meaningful way, but impact on the daily lives of virtually all sufferers.

3.4.1.1 Regression analysis

Despite relatively high secondary care costs, the predominance of high cost but low frequency events meant that further analysis was limited. Regression analysis therefore concentrated on an exploration of the factors associated with high primary care costs.

Logistic regression analysis compared individuals who incurred primary care costs with those who did not and identified comorbidity, knee pain and anxiety as being significant risk factors for incurring medical costs. Interestingly, age, BMI and radiographic evidence of change were not significant factors in the model.

Similar results were observed with the second model (linear regression), which examined factors relevant to the magnitude of primary care costs. This model was able to explain 20% of the observed variance. The importance of pain intensity and comorbidity were confirmed, as was psychological distress (depression). Pain severity has been reported by other investigators as being important in dictating primary care costs (Andersson et al. 1999; Gabriel et al. 1997b), as has depression (Andersson et al. 1999). Once again, obesity and radiographic status were not significant factors within the model. The importance of pain rather than radiographic status in explaining primary care costs, supports the importance of studying symptoms (knee pain) rather than clinical signs (radiographic change).

3.4.2 Comparison with other studies

Costs reported in this study are generally low in comparison with other cost-of-illness studies for OA. However, direct comparison is difficult due to the varied methodologies used. A summary of studies that have examined costs specific to OA is presented Table 49.

Table 49 Summary of previous cost-of-illness studies for OA. (Costs reported in 1996 £ sterling equivalent values).

Source	Costs examined	Method of data collection	Subjects	Main findings	Comment
Lanes et al. (1997) USA	Direct medical costs relating to arthritis only (incl. side-effects of arthritis drugs). Included: Consultations, screening and treatment procedures, medications, surgery, emergency room visits.	Individual utilisation data obtained from the Fallon Community Health Plan. Duration: 1year.	Age ≥ 30 yrs with confirmed diagnosis of OA and ≥ 1 health contact in previous year for OA. n = 10,101.	8,128 (81%) received care for OA during study. Av. cost: £408 per year. 2° care = 46%. Medication = 32% 3.3 visits per person (incl. 1.2 visits to physical therapist.	High service utilisation but very select population (deliberately targeting high service users). Distribution of costs between 2° care, medication and 1° care, similar to current study. Greater use of physical therapy observed (may be USA v UK).
Gabriel et al. (1995) USA	Direct medical, indirect medical and non-medical – total costs (not OA specific). Costing year not specified (assumed to be 1987).	Individual utilisation data from Rochester Epidemiology Project, Olmsted County Health Care Utilisation and Expenditure Database + postal survey. Duration: 1 year.	Aged ≥35 yrs, with a diagnosis of OA between 1975-87. n = 7,889. Controls: residents aged ≥35 yrs without diagnosis of OA. n = 25,893. Postal survey = random sample of 200 from each cohort.	OA: 84% received medical care during 1987. Controls: 82% received care. Av. cost: £2,362, £1,840 respectively. Postal response rate = 50%. Indirect & non-medical costs: £110,517, £88,675 respectively. Excl. wage losses: £326, £66 respectively.	Specification of costs included unclear. Not able to isolate medical costs specific to OA – total costs only.
Gabriel et al. (1997a) USA	Direct medical costs. Compared OA, RA and controls with no arthritis (NA).	Individual utilisation data from Rochester Epidemiology Project, Olmsted County Health Care Utilisation and Expenditure Database. Logistic regression used for comparison of groups.	Diagnosed 1975-87, aged ≥35 yrs. OA: n = 6,742 RA: n = 397 NA: n = 25,904	Av. direct medical cost: OA: £3,068 RA: £4,395 NA: £1,605 OA patients sig. greater costs than NA in arthritis related care, but also virtually all other body systems.	Same cohort as 1995 paper Incremental costs specific to OA identified through comparison of population based cohorts. Identification of individual costs specific to OA not possible.

Table 49 (continued)

Source	Costs examined	Method of data collection	Subjects	Main findings	Comment
Gabriel et al. (1997b) USA	Indirect and non-medical costs Included: Use of non-medical practitioners, travel, home health care, medical equipment, days off work, change in occupation due to ill health	Postal survey. Random sample of above population (200 per group). Logistic regression modelling	Response rate: OA: 116 RA: 123 NA: 94	% incurring these costs: OA: 39% RA: 66% NA: 17% Predictors of costs: Functinal status, pain and presence of arthritis	Poor response rate
Liang et al. (1984) USA	Direct and indirect cost of OA care 1979 US$ Direct costs: Medication, outpatient visits, inpatients stays, surgery, rehab, assistive devices, domestic help. Indirect costs: Days of restricted act'y, days confined to bed, days off work	Random sample of patients registered at Boston Multi-purpose Arthritis Centre who had visited ≥ once in last 5 yrs for arthritis care Included OA and RA patients	303 contacted, 184 volunteered 148 returned at least 1 diary (49 of which were OA patients)	Isolation of OA costs not possible as all data reported as aggregate (OA and RA combined)	Prospectively collected diary data, but led to methodological problems and small OA sample size Complete data for whole yr not possible, costs presented per month Highly selected population
Kramer et al. (1983) USA	Limited to physician visits, hospitalisation and restricted activity days	National Health Interview Survey 1976	RA: 258 OA: 152 Inclusion criteria: Specific diagnosis of OA or RA	For OA patients: Av. visits to GP = 3.5/yr 32% had been hopsitalised at some time. 17% had had surgery. 39% reported limited in activities of daily living.	Community sample but still reliant on physician diagnosis Limited sample and costs examined No attempt made to cost these items

The relatively low costs observed in the current study could be for several reasons. Firstly, the dataset relates to the UK system of health-care. To date, studies examining the cost implications of arthritis have come largely from the USA. Given the very different system of health care provision in the USA, it is important to collect UK data around which policy decisions can be made. A study by Drummond et al. (1995) identified this need when they demonstrated that the cost-effectiveness of using different NSAIDs varied according to the country in which treatment was provided. This difference was largely explained by differences in the cost of laboratory tests and hospitalisation. Given that almost 40% of the direct medical cost associated with the treatment of knee pain was for hospital care, findings could vary considerably between countries.

Clearly another major difference in identifying knee pain costs is the nature of the study population. Previous studies have considered OA costs (all joints) rather than knee-specific costs, have included only those cases with a previous diagnosis of OA (rather than self-reported knee pain) and frequently required evidence of recent health resource use prior to entry (Lanes et al. 1997; Liang et al. 1984). Whilst studies of this kind are informative, they do not estimate the true burden of symptomatic OA (both diagnosed and undiagnosed) in the community. It is also possible that knee-related costs are genuinely modest in comparison with other joints of involvement. Back pain, for example, is associated with considerable morbidity and is common in younger males. Indirect costs alone represent a considerable societal burden. It has been

suggested that indirect costs may account for 93% of the total cost of back pain (van Tulder et al. 1995).

Patients who had had a total knee replacement (TKR) at baseline were excluded from this study. This may have resulted in an underestimation of the true cost of knee OA. Nevertheless, the degree of such bias is likely to be small given the current under-utilisation of knee replacement surgery in this country. Rates are reported as being 0.5-0.7 per 1000 in those aged over 65 years. By contrast, TKR is far more common in the USA where rates of >2 per 1000 have been reported (Dieppe et al. 1999).

Finally, the type of costs considered and the method of applying unit costs vary from study to study. The importance of examining unit resource use rather than average figures for individual procedures was emphasised in this study. Within this population, 3 patients received arthroscopies during the 6-month period of study. Of these patients, 2 incurred costs of £800 each (one for a bilateral operation) and one incurred £2,000. The average cost of an arthroscopy as quoted by the local hospital was £480. Clearly these patients revealed wide variation in actual resource use and were more likely to experience complications resulting in higher medical costs.

3.4.3 Strengths and weaknesses of the study

A major strength of this study was the fact that data were collected prospectively through an examination of GP records. This process was extremely time-consuming but provided unique resource use data for the sample population. In this way estimates were relatively free of recall bias and the impact of study attrition.

Nevertheless, a fundamental concern relating to the study stems from the fact that data were collected within the structure of a randomised controlled trial (RCT). This meant that the study population consisted of volunteers with self-reported knee pain who were enrolled in a 2-year RCT. As a result, the characteristics of this population may well be different from the wider knee pain population and may have reduced the external validity of our findings. Unfortunately, lack of time and resources meant that an examination of the GP notes of non-volunteers was not possible. Previous authors have suggested that non-volunteers may differ from volunteers in that they have fewer overall health-related contacts, but that those contacts that do occur tend to be at a higher cost. In addition, non-volunteers are more likely than volunteers to suffer from serious life-threatening conditions such as cancer (Cronan et al. 1997b).

The method of data collection used by this study also meant that the sample size was considerably smaller than is possible from wide-scale population

surveys (Kramer et al. 1983) or from the examination of well-maintained computerised records (Lanes et al. 1997; Gabriel et al. 1997a). Given the variability of economic data, it is possible that a fully representative sample was not achieved and that very different cost estimates may be obtained from a larger sample population.

The difficulty of ascribing knee-related costs from an examination of medical notes was also problematic. Value judgements were sometimes required and the extent to which the data reflects the true cost of knee pain may be subject to bias. Nevertheless, this represents an ambitious attempt to identify the direct medical costs specific to an individual joint of involvement and the impact of classification errors of this type was explored through sensitivity analysis.

It may be possible that the use of patient questionnaires would have alleviated some of the difficulties of identifying knee-specific costs. However, patients may find it equally difficult to isolate costs relevant to a single joint of involvement in the presence of generalised OA. It is possible that reliance on patient derived data may therefore have introduced greater variability than the methods used (whereby value judgements were limited to 2 individuals). In addition, patient questionnaires pose their own difficulties, most notably the quantification of recall bias (particularly amongst elderly populations) and the need for excessive complexity and length.

Finally, whilst the regression analysis conducted as part of this study provides an interesting insight into some of the factors relating to high medical costs in these patients, it should be recognised that any model is limited by the factors included therein. This study sought to explore factors of a-priori interest and was not intended to be an exhaustive investigation of all relevant factors. It is possible that other factors may be more important in dictating overall costs, such as social class, coping style or the belief in the efficacy of conventional medicine in treating knee pain (Dieppe et al. 1999).

4 Economic Evaluation of trial interventions

4.1 Aims and objectives

This economic analysis was conducted alongside the main RCT (reported in Chapter 2). It is unique in that it provides prospectively collected resource use data over a period of two years. It had two primary objectives:

1. To perform a cost-effectiveness analysis based on outcome measures obtained from the intervention study.

2. To perform a cost-utility analysis in which outcomes were measured in Quality-Adjusted Life-Years.

4.2 Method

4.2.1 Study perspective

Analysis was conducted alongside the RCT to assess whether the provision of a community-based exercise programme was cost-effective in relieving the symptoms and disability of knee pain. Exercise therapy was compared with telephone support, a placebo health food product and no intervention. The study adopted a societal perspective; costs and benefits were examined for both the health care provider and for individuals suffering from knee pain.

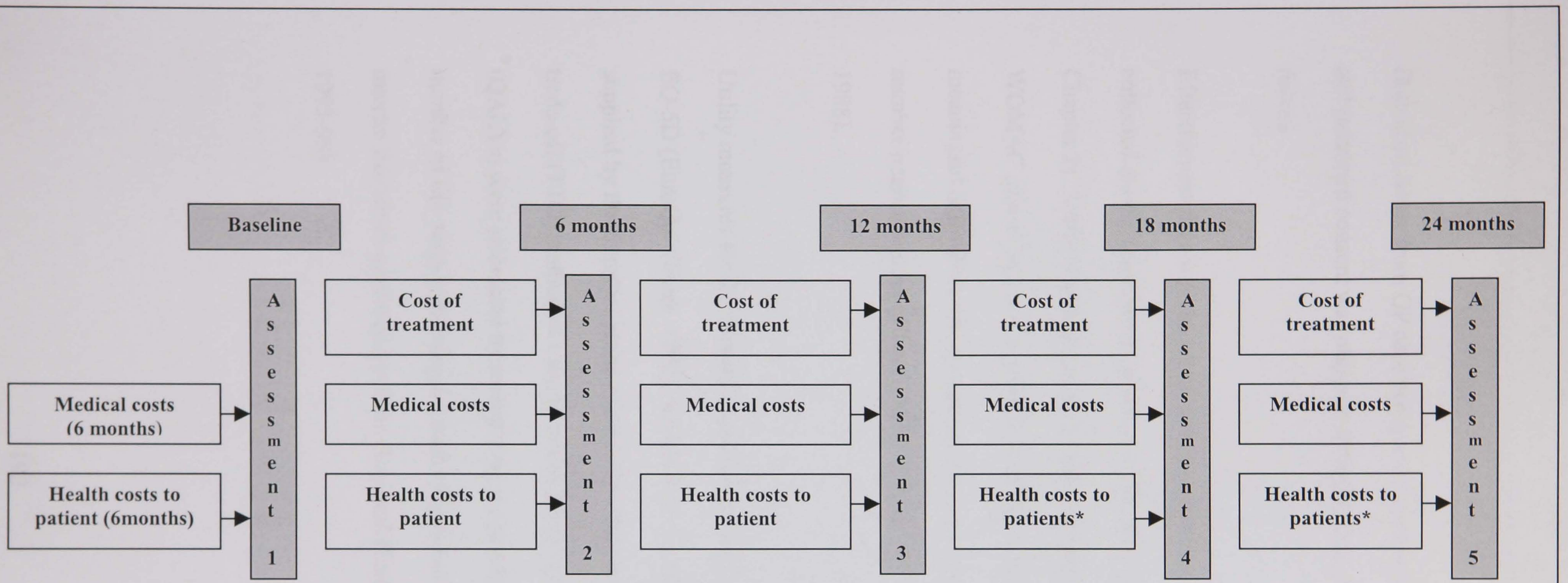
4.2.2 Subjects

Subjects for the economic evaluation were taken from the intervention trial and had self-reported knee pain at baseline. Randomisation was successful and no significant differences were observed between the groups at baseline in demographic or key outcome measures (Table 16).

4.2.3 Materials

Frequency data for resource use were collected through an examination of GP case notes and from patient questionnaires over the 2-year intervention period and for 6 months prior to randomisation (Figure 17).

Figure 17 Summary of data collection.



* The costs of OTC purchases for the final year are modelled based on responses given in the 1st year. Other personal costs are based on actual resource use.

Data abstraction from GP case notes was performed blind to treatment group and informed consent was obtained from patients prior to the accessing of notes.

Effectiveness data were based on self-completion questionnaires and were collected during assessments at six-monthly intervals throughout the trial (see Chapter 2). Units of effectiveness for the economic analysis were based on WOMAC pain scores achieved at 24 months. In order to provide clinically meaningful cost-effectiveness ratios, pain scores were also presented using the number needed to treat statistic (NNT) (Cook and Sackett, 1995; Laupacis et al. 1988).

Utility measures for the cost-utility analysis were obtained using the EuroQol EQ-5D (EuroQol Group, 1990). Scores were calculated using Tariff A1 as supplied by the EuroQol group (Table 50). This tariff is based on the time trade-off (TTO) method of valuing health states. Quality-adjusted life-years (QALYs) were calculated by multiplying the resulting utility scores by the number of life years remaining for each subject (using survival data from interim life tables produced by Trent Regional Health Authority for the years 1993-95).

Table 50 Calculation of EQ-5D utility scores.

EuroQol dimension	Level 2	Level 3
Mobility	0.069	0.314
Self-care	0.104	0.214
Usual activity	0.036	0.094
Pain / discomfort	0.123	0.386
Anxiety / depression	0.071	0.236
Full health = 1	Constant for any dysfunctional state: subtract 0.081	Any dimension scoring 3: subtract 0.269

Example: health state 1 1 2 2 3
Utility score:
1(full health) - 0.081(constant) - 0.036 (usual activity) - 0.123 (pain) - 0.236 (anxiety) -0.269 (constant for level 3) = 0.255

4.2.4 Costs included in the cost analysis

Three main categories of costs were included in the economic analysis:

1. Direct treatment costs – costs incurred by the treatment programmes.
2. Medical costs – secondary and primary care.
3. Costs to patients / family – costs associated with accessing health services (e.g. travel costs, prescriptions and OTC drugs)

Other costs (e.g. personal costs of treatment provision and indirect costs) were examined in a qualitative manner.

4.2.5 Definition of costs

All costs are reported in £ sterling at 1996 prices.

4.2.5.1 Direct cost of treatment provision

Treatment costs were based on frequency data collected during the trial and excluded research costs. This was a pragmatic study, the aim of which was to deliver realistic treatment programmes with a minimum of input from health professionals.

Treatment sessions were approximately 45 minutes (including travel time) for the exercise groups and 2 minutes per call (8 minutes for 1st calls) for the telephone support groups. Exercise participants were given an instruction booklet and a rubber exercise band (Cliniband™). Depending on subsequent muscle strength readings, stronger bands were issued at later visits and damaged bands were replaced.

Exercisers were visited in their own homes and received 7 visits over the two-year period (4 times in the first two months and then once at 6, 12 and 18 months). Subjects in the social support group received monthly calls throughout the two-year period. Allowance was made for the consequences of study attrition in subsequent analysis (actual exercise visits, $\bar{x} = 5.4$; telephone calls, $\bar{x} = 15.2$).

Overheads were included in the hourly labour rate to produce a total hourly rate (including salary, salary on-costs, indirect overheads and capital overheads) (Netten and Dennett, 1996). This resulted in an under-representation of overheads for the telephone support programme since limited client-contact time was involved per person. Nevertheless, the degree of bias was small and should have been compensated for by the fact that telephone calls (normally included in overheads) were costed separately for the telephone intervention. For ease of comparison, personnel time for both exercise therapy and telephone support were based on physiotherapist pay-scales. Alternative costs (based on different personnel pay scales) were considered in sensitivity analysis.

For the purposes of this study, labour costs were classified as variable costs. This meant that the marginal cost of treating one additional patient was represented by the ongoing treatment cost per person (i.e. total cost minus start-up cost). Start-up costs were low for all treatment groups and would be reduced substantially further should a standard exercise programme be developed and disseminated nationwide. Costs incurred in the second year of the intervention programme were discounted by 5% in order to aid comparison with other studies. The impact of applying alternative discount rates (0% to 10%) was explored in sensitivity analysis.

The cost of delivering the placebo health food product was assumed to be its purchase price only, since its inclusion was for research purposes.

4.2.5.2 Personal costs of treatment provision

Personal costs to the individual (loss of leisure time and adverse side effects of the exercise programme) were collected through patient questionnaires and have been documented in a qualitative manner. It was not felt appropriate to attach a monetary figure to these aspects of the programme.

4.2.5.3 Medical costs

The impact of study treatments on the degree to which subjects accessed medical services was explored through an examination of patients' GP notes. The protocol for the examination of notes has already been reported (Chapter 3).

4.2.5.4 Personal medical costs

Personal costs incurred by patients resulting from the need to access medical services were documented. Three types of costs were examined:
i) prescription charges; ii) over-the-counter (OTC) drugs and iii) travel costs incurred whilst travelling to and from the health provider. Further discussion of these costs can be found in Chapter 3.

4.2.5.5 Indirect Costs

Costs associated with lost productivity were not of direct financial relevance to the current study because only 2% of the study population had taken time off work due to knee pain at baseline. Given the small numbers involved, any

possible change in work capacity would have been negligible. Nevertheless, change in work status has been described in a qualitative manner.

4.2.6 Unit costs

Unit cost and frequency of resource use are documented in Table 51 and Table 56 of the results section. Alternative costs may be applied as required.

4.2.7 Data management

4.2.7.1 General data management

All data were entered onto a customised database (Microsoft® Access 97) and unit costs were applied in SPSS for Windows version 8.0 (SPSS Inc., Chicago, IL). Costs for each 6-month period were calculated separately, resulting in five individual cost periods as follows.

Baseline costs:	-6 months to 0 months
Period 1 costs:	0 months to 6 months
Period 2 costs:	6 months to 12 months
Period 3 costs:	12 months to 18 months
Period 4 costs:	18 months to 24 months

Data relating to the first 18 months were collected by two researchers alongside the intervention study. Due to time and financial constraints, data relating to the final 12-month period were collected as part of a separately funded project by 3 different researchers. In order to ensure consistent results, training was provided along with regular monitoring sessions. Any bias that may have been

introduced by this process would have been equally distributed between the treatment groups.

4.2.7.2 Total costs versus change in costs

Costs included in the economic analysis represent total costs over the 2-year intervention period. Total costs were chosen rather than change in costs for two main reasons:

a) It allowed the inclusion of all study data. Baseline costs were collected for a 6-month period only and change in cost calculations would therefore have been possible for two periods of six months only (period 2 and period 5).
b) Total costs are potentially more informative to health policy decision-makers.

4.2.7.3 Handling of missing values

The identification of medical resource use was not influenced by study attrition as details were collected through an examination of GP notes. However, data for the final 12-month period were unavailable for 101 (13%) individuals because either informed consent was not obtained in order to re-examine case notes, or the patients' notes were no longer available. Missing values for these individuals were carried forward from the previous period corresponding to the same time of year (Rutten-van Molken et al. 1995; Rutten-van Molken et al. 1994). This meant that data for period 4 were obtained by carrying forward values from period 2. Likewise, data for period 5 were taken from period 3.

Individuals without data for the final 12-month period were evenly distributed between the treatment groups and should not have impacted on subsequent between group comparisons.

4.2.7.4 Handling of uncertainty

Sensitivity analysis has been used to examine the implications of uncertainty surrounding frequency of resource use, unit costs and patient outcomes (Briggs and Sculper, 1995). In addition, confidence intervals provide an indication of the variability of patient-specific data for both costs and benefits. Confidence intervals have been reported using standard parametric tests. This was felt to be appropriate as recent authors have suggested that simple parametric techniques are more robust in handling skewed cost data than had previously been recognised (Thompson and Barber, 2000; Lord et al. 1999). Nevertheless, results were confirmed using non-parametric bootstrapping techniques for the final incremental cost-effectiveness analysis.

4.2.8 Statistical analysis

A significance level of 5% was employed throughout the study and confidence intervals were reported at the 95% level. An indication of clinical significance was addressed by using the NNT statistic as the measure of treatment efficacy (Cook and Sackett, 1995; Laupacis et al. 1988). The NNT represents the number of patients who need to be treated in order to achieve a ≥ 50%

improvement in self-reported knee pain at 24 months. For patient-specific outcome data, the change in WOMAC pain score was used.

4.2.8.1 Power

As is common with studies of this type, power calculations were performed using the primary outcome measure for the intervention study (reported in Chapter 2). However, cost data provide unique difficulties for statistical analysis, being highly variable, usually demonstrating a skewed distribution and having a large number of individuals with zero cost. Retrospective power calculations based on direct medical costs observed at 12 months suggested that the current study had only 34% power to detect an effect size of 0.12 in primary care costs (26% power for total medical costs) (nQuery Advisor 3.0). Whilst conclusions relating to the economic evaluation of this trial should be made with caution in the light of this low power (Briggs, 2000), these data represent an ambitious attempt to document the economic impact of exercise therapy.

As the study had insufficient power to detect between group cost differences, the presentation of data for individual costs (direct intervention costs, medical costs and personal costs) was limited to descriptive statistics. Analysis of between group differences was presented for the combined cost and outcome data (ICERs) using non-parametric bootstrapping techniques to produce a distribution on the C/E plane and an 'acceptability curve' (Lothgren and

Zethraeus, 2000; Briggs and Fenn, 1998). It is hoped that the presentation of results in this way will provide meaningful and readily interpretable data for health policy decision-makers.

4.2.8.2 Incremental cost-effectiveness analysis

Incremental cost-effectiveness ratio (ICER) calculations were performed using the equations outlined overleaf. Two effectiveness measures were used; the first provides patient-specific data (change in WOMAC pain), the other provides a clinically relevant summary statistic based on group comparisons (NNT). The number needed to treat is based on a comparison of the intervention group and the no intervention control group. As such, it is already incremental in nature. Equally, the treatment costs incurred by the no intervention group were zero. Incremental treatment costs thus reflect the costs incurred by each group during the period of the trial.

Equation 5 Cost-effectiveness formulae for change in WOMAC pain (C=cost; E=efficacy; C/E = cost effectiveness ratio).

$$C/E = \frac{C_{Intervention} - C_{Control}}{E_{Intervention} - E_{Control}}$$

Equation 6 Cost-effectiveness formulae for NNT (C=cost; E=efficacy; C/E = cost effectiveness ratio; NNT=number needed to treat;

NNT = 1/E $_{\text{Intervention}}$ - E_{Control}*).*

$$C/E = NNT \times (C_{Intervention} - C_{Control})$$

4.2.8.3 Interpretation of ICERs

Ratio statistics such as those represented by incremental cost-effectiveness ratios (ICERs) present difficulties for standard methods of dealing with uncertainty (Briggs and Fenn, 1998). Various suggestions have been made in the health economics literature as to the most appropriate method to be used (Tambour et al. 1998; Briggs and Fenn, 1998; Chaudhary and Stearns, 1996; van Hout et al. 1994; O'Brien et al. 1994). One of the simpler and more robust methods to have been discussed is the non-parametric bootstrap (Lothgren and Zethraeus, 2000; Efron and Tibshirani, 1993). This computer-intensive technique involves the repeated re-sampling of the original dataset

and does not require assumptions of normality (Johnston et al. 1999). Bootstrap estimates have been used in the current study to produce an 'acceptability curve'. The resulting probability curve gives an estimate of the precision of the cost-effectiveness ratios and the probability that the ratio of costs and benefits falls within acceptable cost limits (Briggs and Fenn, 1998; van Hout et al. 1994).

Non-parametric bootstrap techniques require patient-specific outcome data for both costs and benefits. As such, ratios have been presented using the change in WOMAC pain score rather than the NNT (which is a summary statistic). Since this change score results in a negative value for an improvement in knee pain, the resulting C/E plane is slightly different to that commonly reported in the literature (Figure 6). Using change scores as the measure of effectiveness, it is quadrant IV that represents an improvement in health outcome at some additional cost. This is usually represented by quadrant I on the C/E plane. Points presented on the resulting C/E plane are the result of the re-iterative process of the bootstrap technique; each point representing a new bootstrap sample.

Bootstrapping is a 3-stage process. Firstly, a sample of patient-specific costs and outcome data is taken (with replacement) from the existing dataset. Mean cost and effectiveness estimates are then calculated for the resulting sample. This process is repeated for each of the compared interventions. Finally, the ICER is calculated (Δ cost / Δ effect). Repeating this process many times

(usually >1,000 times) produces a series of bootstrap estimates, which are an empirical estimate of the sampling distribution of the ICER statistic (Briggs and Fenn, 1998). From this data, it is possible to present confidence intervals for the ICER distribution (Briggs et al. 1997; Chaudhary and Stearns, 1996). However, it has been argued that a two-sided confidence interval is inappropriate for economic analysis when the appropriate hypothesis is one-sided (i.e. what is the probability that the new intervention is not cost-effective?) (Briggs and Fenn, 1998). The presentation of data as an 'acceptability curve' resolves this issue and has the added advantage of quantifying the probability that an intervention is cost-effective across a range of potential ceiling values (Lothgren and Zethraeus, 2000). This intuitive manner of presenting cost data does not require the researcher to make assumptions on behalf of the health decision-maker, as the probability that an intervention is cost-effective is presented for a range of ceiling values, and the range of costs and benefits presented in the curve is dictated by the original dataset from which the bootstrap samples are drawn.

4.3 Results

4.3.1 Cost of treatment provision

4.3.1.1 Direct treatment costs

Costs to the health provider for the two-year intervention period were £112 for the exercise programme, £61 for telephone support and £7 for the dolomite control group. Full details are tabulated (Table 51). For exercise therapy, the majority of costs were incurred during the first 6 months of treatment provision (representing 4 treatment visits). Subsequent periods incurred comparable costs to those of the telephone intervention.

4.3.1.2 Personal costs

Personal costs incurred as a result of direct treatment provision were limited to the opportunity costs of time spent in therapy for all treatment groups. For the exercise groups this was up to 20 minutes per day (depending on treatment adherence) and for the telephone support groups approximately 2 minutes per month. All necessary equipment was provided for the exercise programme and treatments were delivered to subjects in their own homes. It has not been possible to attach a monetary figure to the opportunity cost of time spent exercising (particularly as many volunteers reported exercising whilst performing other activities). Details have been documented in a qualitative manner only (Table 52).

Table 51 Summary of 2-year treatment costs by treatment type.

	Unit cost £	Year 1 Units	Year 1 £	Year 2* Units	Year 2* £	Total £/person
EXERCISE						
Start-up costs						
Initial training	18 / hour	2 days	260.00			
Dev't of programme	18 / hour	1 month	2,730.00			
Start-up cost / person			6.35			
Ongoing costs / person						
Personnel – treatment	18 / hour	3hr 22 min	58.05	49.5 min	14.10	
Personnel – admin	18 / hour	1hr 10 min	21.00	17 min	4.85	
Travel	0.37 / mile	8.6 miles	3.18	2.2 miles	0.77	
Equipment						
Booklet	0.30 each	1 booklet	0.30	0 booklets	-	
Exercise band	1.76 / m	2.1m	3.70	0.1m	0.17	
Total £ / person			**92.58**		**19.89**	**112.47**
TELEPHONE						
Start-up costs						
Initial training	18 / hour	1 day	130.00			
Start-up cost / person			0.33			
Ongoing costs / person						
Personnel – phone contact	18 / hour	20.4 min	6.12	16 min	4.56	
Personnel – admin	18 / hour	1hr 27 min	26.10	1hr 20 min	22.80	
Telephone charges	0.04 / min	20.5	0.82	16 min	0.60	
Total £ / person			**33.37**		**27.96**	**61.33**
PLACEBO – DOLOMITE						
Tablet cost	1.69 / bottle	2 bottles	3.38	2 bottles	3.20	
Total £ / person			**3.38**		**3.20**	**6.58**

* Year 2 discounted by 5%.

Table 52 Personal time costs incurred by subjects in the exercise programme.

Time taken per session	n	< 10 minutes (%)	10 –20 minutes (%)	> 20 minutes (%)
1st 6 months	317	57 (18)	145 (46)	115 (36)
2nd 6 months	235	51 (22)	114 (48)	70 (30)
3rd 6 months	207	46 (22)	92 (44)	69 (33)
Days per week	**n**	**5 to 7 days (%)**	**3 to 4 days (%)**	**< 3 days (%)**
1st 6 months	334	237 (71)	43 (13)	54 (16)
2nd 6 months	266	181 (68)	29 (11)	56 (21)
3rd 6 months	227	161 (71)	24 (11)	42 (18)

From an examination of patients' GP notes, adverse effects relating to the exercise programme were noted in 9 consultations during the 1st year (positive effects being reported during one visit).

4.3.2 Medical costs

4.3.2.1 Baseline medical costs

Baseline medical costs were documented in Chapter 3. Costs by treatment group at baseline are documented in Table 53. As is common with cost data, relatively high variation exists between the treatment groups. This is particularly so for hospital costs. Mean hospital costs in the exercise only group were high because a single outlier incurred costs of £24,400. Hospital costs incurred by the no intervention group were low compared to the other groups ($\bar{x}$ = £68.50).

Table 53 Baseline medical costs by treatment group.

GP COSTS **Group**	**Mean (s.d.) (£)**	**Median (£)**	**1st quartile (£)**	**3rd quartile (£)**	**Max (£)**
Ex & Tel (n = 117)	23.56 (26.5)	20.00	0.00	39.00	130
Ex, Tel & Dol (n = 109)	30.17 (31.8)	20.00	10.00	50.00	170
Exercise (n = 226)	30.20 (33.7)	20.00	10.00	41.25	178
Telephone (n = 154)	28.58 (30.5)	22.50	0.00	40.00	180
Dolomite (n = 77)	27.38 (28.0)	20.00	10.00	35.00	140
Nothing (n = 76)	28.36 (27.8)	20.00	10.00	40.00	130
PRESCRIBED DRUG COSTS **Group**	**Mean (s.d.) (£)**	**Median (£)**	**1st quartile (£)**	**3rd quartile (£)**	**Max (£)**
Ex & Tel (n = 117)	70.60 (107.0)	26.01	4.32	109.53	604
Ex, Tel & Dol (n = 109)	83.21 (128.2)	38.72	4.86	105.41	750
Exercise (n = 226)	74.43 (120.7)	30.28	4.33	101.51	951
Telephone (n = 154)	78.42 (150.3)	29.06	5.07	75.84	1,200
Dolomite (n = 77)	69.89 (99.6)	34.43	9.04	66.15	513
Nothing (n = 76)	69.70 (117.0)	24.52	5.20	75.35	752
HOSPITAL COSTS **Group**	**Mean (s.d.) (£)**	**Median (£)**	**1st quartile (£)**	**3rd quartile (£)**	**Max (£)**
Ex & Tel (n = 117)	125.9 (510.3)	0	0	188.40	3,960
Ex, Tel & Dol (n = 109)	148.5 (393.8)	0	0	560.00	2,340
Exercise (n = 226)	235.0 (1,682)	0	0	146.00	24,400
Telephone (n = 154)	99.01 (345.5)	0	0	140.00	2,340
Dolomite (n = 77)	114.1 (323.5)	0	0	256.00	1,800
Nothing (n = 76)	68.50 (369.6)	0	0	80.00	3,100
TOTAL MEDICAL COSTS **Group**	**Mean (s.d.) (£)**	**Median (£)**	**1st quartile (£)**	**3rd quartile (£)**	**Max (£)**
Ex & Tel (n = 117)	220.0 (577.3)	74.56	14.13	173.04	4,619
Ex, Tel & Dol (n = 109)	261.9 (459.0)	110.64	29.44	196.01	2,645
Exercise (n = 226)	339.6 (1,744)	79.16	26.64	212.77	25,366
Telephone (n = 154)	206.0 (390.7)	75.62	21.79	194.69	2,393
Dolomite (n = 77)	211.3 (356.7)	78.77	35.46	193.20	1,856
Nothing (n = 76)	166.6 (407.6)	74.05	21.59	150.36	3,331

4.3.2.2 Medical and societal costs incurred during the trial

Total primary care costs were almost £342,000 for the 24-month treatment period, with a mean cost of £450 per person. The inclusion of hospital costs resulted in an almost three-fold increase to just over £960,000 ($\bar{x}$ = £1,266). Summary details are tabulated (Table 54). Costs incurred during year 2 were discounted by 5%.

Table 54 Summary of medical and societal costs incurred during the trial period.

n = 759	Year 1	Year 2*	24 Months
PRIMARY CARE COSTS			
(GP + GP prescribed drugs)			
Total	168,750	173,108	341,858
Mean (s.d.)	222 (278)	228 (280)	450 (548)
Median	135	137	274
TOTAL MEDICAL COSTS			
(Primary + secondary care costs)			
Total	480,896	479,724	960,619
Mean (s.d.)	634 (2,004)	632 (1,889)	1,266 (3,688)
Median	206	216	478
SOCIETAL COSTS			
(Total medical costs + personal costs)			
Total	503,514	501,511	1,005,025
Mean (s.d.)	663 (2,011)	661 (1,895)	1,324 (3,699)
Median	230	242	554

*Costs discounted by 5% in year 2.

4.3.2.3 Impact of study interventions on medical costs

Between group differences in medical costs at 24 months are presented in (Table 55). In addition to mean costs, median and maximum values are presented for interest. The extremely high maximum values for hospital costs in the 'exercise only' and the 'dolomite' groups reflect the cost of treating two individuals who required intermittent inpatient care throughout the 24-month period.

Table 55 Medical costs by treatment group over 24 months.

GP COSTS (£)					
Group	**Mean (s.d.)**	**Mean difference***	**95% CI**	**Median**	**Max**
Ex & Tel (n = 117)	107 (80)	-14	-58, 29	88	384
Ex, Tel & Dol (n = 109)	126 (134)	5	-39, 49	88	816
Exercise (n = 226)	118 (110)	-3	-42, 36	89	712
Telephone (n = 154)	112 (96)	-9	-50, 32	86	519
Dolomite (n = 77)	105 (75)	-16	-64, 31	78	274
Nothing (n = 76)	121 (98)	–	–	93	435
GP PRESCRIBED DRUG COSTS (£)					
Group	**Mean (s.d.)**	**Mean difference***	**95% CI**	**Median**	**Max**
Ex & Tel (n = 117)	297 (400)	-76	-286, 134	158	2,872
Ex, Tel & Dol (n = 109)	372 (569)	-1	-214, 212	206	3,777
Exercise (n = 226)	331 (431)	-42	-231, 146	169	2,513
Telephone (n = 154)	341 (589)	-32	-232, 167	124	4,194
Dolomite (n = 77)	307 (384)	-66	-296, 164	163	1,681
Nothing (n = 76)	373 (612)	–	–	156	3,415

Table 55 (continued).

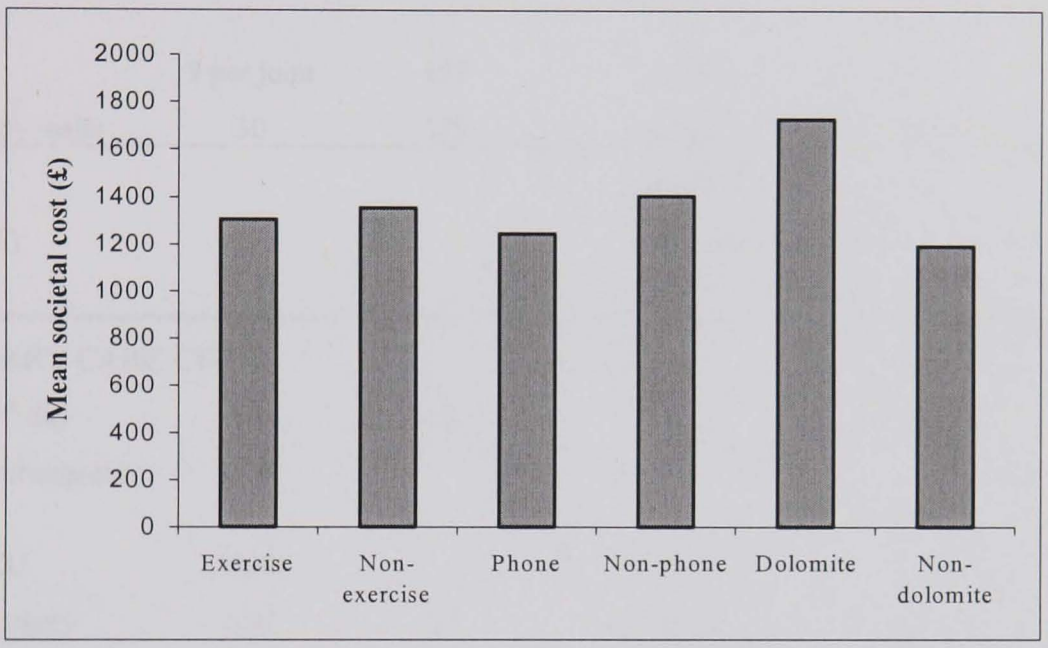
SECONDARY CARE COSTS (£)					
Group	**Mean (s.d.)**	**Mean difference***	**95% CI**	**Median**	**Max**
Ex & Tel (n = 117)	827 (1,972)	238	-1,254, 730	40	9,900
Ex, Tel & Dol (n = 109)	896 (2,020)	307	-1,207, 820	82	13,098
Exercise (n = 226)	737 (2,899)	148	-1,195, 491	78	39,238
Phone (n = 154)	557 (1,260)	-32	-1,452, 1,388	40	7,644
Dolomite (n = 77)	1,653 (9,165)	1,064	-574, 2,701	78	80,223
Nothing (n = 76)	589 (1156)	–	–	100	5,040
PRIMARY CARE COSTS (£)					
Group	**Mean (s.d.)**	**Mean difference***	**95% CI**	**Median**	**Max**
Ex & Tel (n = 117)	404 (446)	-90	-321, 140	287	3,241
Ex, Tel & Dol (n = 109)	498 (653)	4	-230, 238	332	4,121
Exercise (n = 226)	449 (480)	-45	-253, 162	262	2,744
Phone (n = 154)	452 (628)	-42	-261, 178	265	4,276
Dolomite (n = 77)	412 (414)	-82	-335, 171	263	1,749
Nothing (n = 76)	494 (660)	–	–	265	3,522
TOTAL MEDICAL COSTS (£)					
Group	**Mean (s.d.)**	**Mean difference***	**95% CI**	**Median**	**Max**
Ex & Tel (n = 117)	1,231 (2,208)	147	-1,401, 1,696	478	13,071
Ex, Tel & Dol (n = 109)	1,394 (2,387)	310	-1,261, 1,881	470	14,200
Exercise (n = 226)	1,186 (3,101)	103	-1,291, 1,496	494	41,738
Phone (n = 154)	1,009 (1,499)	-74	-1,547, 1,400	433	7,754
Dolomite (n = 77)	2,065 (9,154)	982	-718, 2,682	501	80,377
Nothing (n = 76)	1,083 (1,583)	–	–	527	8,312

* Mean difference calculated using no intervention control group as comparator.

4.3.2.3.1 *Analysis by factor*

Between group comparisons were repeated by factor (exercise, telephone and dolomite), with similar results (Figure 18).

Figure 18 Mean societal costs by treatment type (exercise, telephone and dolomite)



A breakdown of unit of resource use and total costs are tabulated for the exercise and non-exercise groups (Table 56). Subjects in the exercise groups incurred marginally lower costs than those in the non-exercise groups: -£3 for total primary care costs, -£45 for total medical costs and -£50 for societal costs. Since these differences were minimal and had extremely wide confidence intervals, cost-effectiveness analysis was based on direct costs of treatment provision only. Medical costs were subsequently included in a secondary analysis to produce an 'acceptability curve' based on re-sampled bootstrap data (Lothgren and Zethraeus, 2000; van Hout et al. 1994).

Table 56 Frequency of resource use and total medical costs over the 24-month study period – exercise versus non-exercise (costs in year 2 discounted by 5%).

	Unit cost £	Unit resource use	Total cost (£) Exercise n = 452	Unit resource use	Total cost (£) Non-exercise n = 307
GP COSTS					
Consultations	10	4,084	39,825	2,681	26,137
Telephone contact	5	53	258	28	137
Investigations / treatments	5	1,275	6,209	916	4,449
X-rays	9 per joint	157	1,373	112	977
Domicilliary visits	30	179	5,243	96	2,802
TOTAL			**52,908**		**34,503**
Mean (s.d.)			**117 (110)**		**112 (92)**
Median			89		88
SECONDARY CARE COSTS					
Inpatient 1st day	500	149	277,830	84	203,310
Inpatient subsequent days	300				
Days in ICU	1,000	1	1,000	2	1,950
Daycase surgery	480	56	26,160	30	13,968
Outpatient new referral	100	224	21,845	163	15,880
Outpatient follow-up	40	813	31,680	550	21,408
A&E	42	58	2,402	33	1,350
TOTAL			**360,917**		**257,866**
Mean (s.d.)			**799 (2,485)**		**840 (4,712)**
Median			77		78
GP PRESCRIBED DRUGS					
NSAIDs $\bar{x}$ (s.d.)			15,558 (34.42)		10,401 (33.88)
Topical rubs / gels $\bar{x}$ (s.d.)			2,695 (5.96)		2,120 (6.91)
Analgesics $\bar{x}$ (s.d.)			5,591 (12.37)		3,414 (11.12)
Gastrointestinal drugs $\bar{x}$ (s.d.)			20,324 (44.97)		14,804 (48.22)
Other arthritis related drugs $\bar{x}$ (s.d.)			987 (2.18)		761 (2.48)
TOTAL ARTHRITIS DRUGS			**45,154**		**31,500**
Mean (s.d.)			**100 (192)**		**103 (222)**

Table 56 (continued).

	Total cost (£) Exercise	Total cost (£) Non-exercise
TOTAL UNRELATED DRUGS	**104,855**	**72,938**
Mean (s.d.)	**232 (376)**	**238 (460)**
TOTAL DRUGS	**150,010**	**104,439**
Mean (s.d.)	**332 (461)**	**340 (550)**
TOTAL PRIMARY CARE COSTS	**202,917**	**138,941**
Mean (s.d.)	**449 (519)**	**453 (598)**
Median	285	265
TOTAL MEDICAL COSTS	**563,830**	**396,790**
Mean (s.d.)	**1247 (2,725)**	**1,293 (4,770)**
Median	480	477
TOTAL SOCIETAL COSTS (Medical + personal costs)	**589,270**	**415,755**
Mean (s.d.)	**1,304 (2,744)**	**1,354 (4,773)**
Median	532	568

4.3.3 Indirect costs

Only 18 (2.3%) subjects reported having taken time off work due to knee pain at baseline. By 24 months this figure had fallen to 8 (1.2%) and was evenly distributed between the 6 treatment groups. It is most likely that any reduction reflected a change in work status and the consequences of study attrition rather than the direct consequences of treatment provision and indirect costs were not therefore included in the cost-effectiveness analysis.

4.3.4 Incremental cost-effectiveness analysis

The primary cost-effectiveness measure was based on costs and outcomes achieved at 24 months. Two incremental ratios are presented. The first is

based on the cost of achieving a one-point reduction on the WOMAC pain scale and the second is based on the NNT statistic (Table 57). Costs incurred by the combined intervention groups reflect the provision of multiple treatments. As a result, the cost of providing the exercise programme in isolation is best estimated from the exercise only group; amounting to £108 per unit change on the WOMAC pain scale or £1,024 per patient showing a ≥50% improvement. The provision of dolomite tablets was consistently the most cost-effective form of treatment, costing just £129 to achieve at least a 50% reduction in pain (a reflection of the extremely low costs incurred by this intervention, rather than superior efficacy).

Table 57 Incremental cost-effectiveness ratios based on WOMAC pain and NNT scores at 24 months, figures rounded to nearest whole pound).

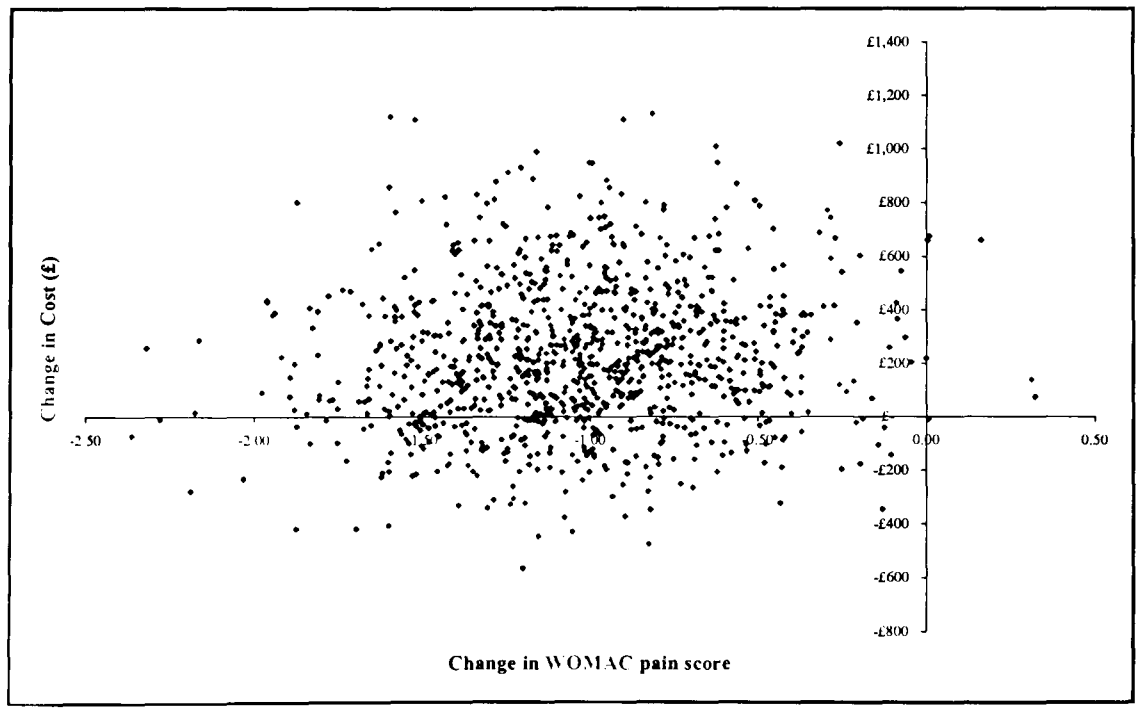
	Direct treatment cost (£)	Δ WOMAC pain	C/E ratio * WOMAC pain (£)	NNT ≥ 50%	C/E ratio# NNT (£)
Group 1 Exercise & Telephone (n=121)	173.80	1.49	117	7.7	1,338
Group 2 Ex, Tel & Dolomite (n=114)	180.38	1.07	169	12.7	2,291
Group 3 Exercise (n=235)	112.48	1.04	108	9.1	1,024
Group 4 Telephone (n=160)	61.33	0.45	136	25.5	1,564
Group 5 Dolomite (n=78)	6.58	0.75	9	19.6	129
Group 6 No intervention (n=78)	N/A	N/A	N/A	N/A	N/A

* Cost of achieving a one point improvement on the WOMAC pain score.
# Cost of achieving a clinically meaningful improvement in at least one individual compared with the no intervention control group.

4.3.5 Acceptability curve

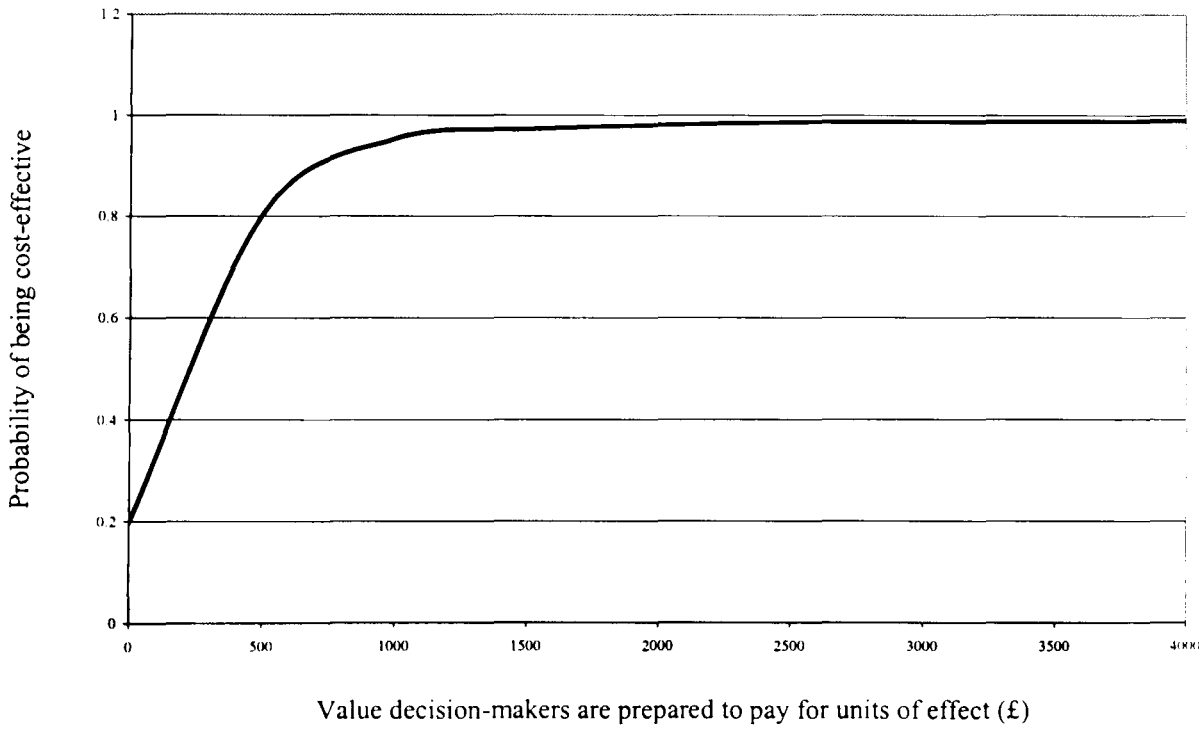
Point estimates for the ICER presented thus far are based on direct intervention costs only. In order to assess the importance of medical and personal costs and to provide an indication of the variability of the dataset, all costs were included in a subsequent bootstrap analysis. This analysis is based on a comparison of WOMAC change in pain scores for the exercise only group (group 3) compared with the no intervention control group (group 6). A negative effect score represents a reduction in knee pain, and therefore an improvement overall. Estimates of incremental cost-effectiveness resulting from the bootstrap analysis are presented on the C/E plane below (Figure 19).

Figure 19 Cost-effectiveness plane (showing bootstrapped ICERs)



Clearly, the majority of the new ICER estimates fall within quadrant IV (796/1000). These represent estimates whereby the intervention produces additional health benefits, but these are achieved at a greater cost. The number of points in each of the four quadrants is used to calculate the 'acceptability curve' (Figure 20). This curve intersects with the y-axis at 0.2, suggesting that there is a 20% chance that the programme could deliver a one-point improvement in knee pain at no additional cost. However, with an investment of approximately £500 per unit of effect, the probability of a successful outcome is increased to 80%.

Figure 20 Acceptability curve (exercise only compared with no intervention control). Based on total societal costs and change in WOMAC pain.



4.3.6 Sensitivity analysis

Sensitivity analysis was performed in order to test a range of assumptions relating to both the costs and consequences of the study treatments. ICERs are presented based on the NNT as the unit of outcome.

4.3.6.1 Sensitivity analysis - costs

For the sake of clarity, cost comparisons were based on comparison of the exercise only group (Group 3) with the no intervention control group (Group 6).

Personnel costs represented the single most important factor in determining direct treatment costs. Cost-effectiveness estimates were based on physiotherapy pay-scales. This could have led to a potential over-estimation of the actual implementation costs if physiotherapy assistants implemented the programme. The use of physiotherapy assistants would reduce the 2-year implementation costs from £113 per person to £71.

A further source of uncertainty is the potential impact of the treatment interventions on subsequent medical costs. Sensitivity analysis was used to explore the impact of a change in primary care costs. Results of the current study were limited by lack of power and confidence intervals for the mean difference in costs show wide variation ranging from a saving of £253 to an additional cost of £162.

4.3.6.2 Sensitivity analysis - benefits

Participation in the current study was the result of active recruitment following completion of a postal questionnaire. Upon wide-scale implementation, the programme would be delivered to knee pain sufferers who presented to their GP. In order to explore the possible impact of this, results relating to individuals who consulted their GP for knee pain in the 6 months prior to participation in the study where analysed separately (n = 217). Comparison of exercise and non-exercise groups for those attending surgery showed a large difference in effect size (0.51 versus 0.10). This meant that the NNT for the self-referred group was 6.1 with a corresponding C/E ratio of £686.

A factor with the potential to impact both costs and benefits is that of treatment adherence. As reported in Chapter 2, effect sizes for those volunteers who adhered well to the programme were considerably higher than for those who did not (0.42 versus 0.16). Direct treatment costs were higher for those completing the programme because all 7 treatment visits were delivered. Nevertheless, the additional cost of these visits was compensated for by improved outcomes (NNT = 6). In the absence of data relating to the number of treatment visits received by the low adherence group, sensitivity analysis assumed that an average of three out of the 7 treatment visits were delivered. This would result in a cost per person for the low adherence group of approximately £77 and a C/E of £1,632.

Finally, baseline pain was found to be a strong predictor of improvements in knee pain at 24 months. The potential impact of baseline pain levels on subsequent C/E ratios was explored using 3 categories of pain (tertiles). Those individuals who scored 5 or less for WOMAC pain at baseline (range 0 – 20) were less likely to report improved outcomes at 24 months (NNT = 19). By contrast, those with baseline pain scores greater than 9, were more likely to benefit from the exercise programme (NNT = 8.6).

Whilst these effects have been reported separately, it should be recognised that their effects are not mutually exclusive. Rather, they may be seen as possible indicators of symptomatic knee pain. It is possible that an individual with severe pain would be more likely to consult their GP for treatment and may also be more likely to adhere to the exercise regime once implemented.

Given that a total knee replacement operation costs approximately £5,000, it would appear that the exercise programme provides a cost-effective addition to the medical management of knee pain. Variation of the above parameters largely resulted in modest changes to C/E ratios. The largest change was elicited by a possible change in primary care costs based on the upper 95% CI (resulting in increased costs of £162 per person). Even this extreme case resulted in a C/E ratio of just £2,500. Threshold analysis suggested that the direct costs for provision of the exercise programme would have to increase to

£550 per person or the NNT increase to 44.5 in order produce C/E ratios comparable to the direct cost of surgery.

Table 58 Sensitivity analysis.

Source of uncertainty	Min. value	Max. value	Value used	Min. C/E ratio (£/person)	Max. C/E ratio (£/person)
Uncertainty in costs*					
Personnel costs	Physio. Assistant (£10.50/hr)	—	Physio. (£18.00/hr)	£ 647 (£ 71.14)	—
Δ primary care costs	Lower C.I.# (-£253)	Upper C.I.# (£162)	Not used	-£ 1,279 (-£140.52)	£ 2,498 (£ 274.48)
Discount rate: Costs	0%	10%	5%	£ 1,033.03 (£ 113.52)	£ 1,014.01 (£ 111.43)
Uncertainty in benefits+					
Self referred patients (n = 217)	NNT = 6.1	—	All subjects NNT = 12.6	£686 (112.48)	—
Treatment adherence	Low adherence NNT = 21.3 Cost/person £76.64	High adherence NNT = 6 Cost/person £142.21	Actual adherence NNT = 12.6 Cost/person £112.48	£1,632 (£76.64)	£853.26 (£142.21)
Baseline pain	WOMAC pain <5 NNT = 19	WOMAC pain >9 NNT = 8.6	All subjects NNT = 12.6	£2,137 (£112.48)	£967 (£112.48)

*C/E ratios for costs based on comparison of group 3 (exercise) versus group 6 (no intervention) (C/E = £1,024). Effectiveness based on NNT for ≥ 50% improvement at 24 months (9.1 people).
95% C.I. for mean difference in primary care costs.
+ C/E ratios for benefits based on a comparison of combined exercise and non-exercise groups.

4.3.7 Cost-utility analysis

No differences were observed between the exercise and the non-exercise groups in quality-adjusted life-years (QALYs) at either 6 or 24 months (Table 59). QALY scores for the two groups were so similar that cost-utility analysis was not performed and the resulting analysis becomes one of cost-minimisation. The exercise therapy was provided at an additional cost of £113 per person treated (direct treatment costs) and was therefore less cost efficient than normal care in producing improvements in quality-of-life.

Table 59 Change in QALY at 6 and 24 months (exercise versus non-exercise).

QALYs	Baseline QALY	Mean Δ	Mean difference	95% C.I. mean difference
6 months				
Exercise (n = 452)	12.93	0.75	-0.17	-0.72, 0.38
Non-exercise (n = 307)	12.56	0.92		
24 months				
Exercise (n = 452)	12.93	0.61	-0.09	-0.83, 0.63
Non-exercise (n = 307)	12.56	0.70		

The above QALY scores were derived from 5 domains, each with a range from 1 to 3. As anticipated, baseline scores revealed difficulties with pain, mobility and activities of daily. However, between group comparisons revealed no difference in change scores between the exercise and non-exercise groups at 24 months for any of the 5 domains (Table 60).

Table 60 EQ-5D domains at 24 months – exercise versus non-exercise

	Baseline mean (s.d)	Mean Δ from baseline	Mean difference	95% CI mean difference
Mobility				
Exercise	1.63 (0.5)	-0.05	-0.04	-0.11, 0.05
Non-exercise	1.61 (0.5)	-0.01		
Self-care				
Exercise	1.12 (0.3)	0.04	0.03	-0.02, 0.08
Non-exercise	1.12 (0.3)	0.01		
Usual activities				
Exercise	1.59 (0.5)	-0.09	-0.08	-0.15, 0.02
Non-exercise	1.60 (0.5)	-0.01		
Pain				
Exercise	2.05 (0.3)	-0.10	0.01	-0.07, 0.09
Non-exercise	2.09 (0.4)	-0.11		
Depression				
Exercise	1.38 (0.5)	-0.02	0.02	-0.05, 0.1
Non-exercise	1.39 (0.5)	-0.04		

4.4 Discussion

4.4.1 Main findings

The direct cost of the 2-year exercise programme was £112 per person. The majority of this amount was incurred during the initial 6-month training phase of the programme. Subsequent visits were principally designed to encourage continued participation and to ensure that the exercises were performed correctly. The relative benefits of a home-visit every six months versus monthly telephone contact are difficult to assess from this trial. However, it is conceivable that both could have fulfilled a similar role. Data from the trial suggested that similar resource use was intrinsic to both modes of treatment provision in later months.

The direct treatment cost of the 2-year telephone intervention was roughly half that of the exercise programme. The very low cost of this intervention has led to claims of cost-effectiveness by other researchers (Weinberger et al. 1993). However, efficacy data from the current trial failed to show a significant improvement in health status. Similarly, the benefits observed from the use of the placebo health food product were non-significant and the cost-effectiveness ratio should therefore be treated with caution. The apparent cost-effectiveness of this product is the result of its very low cost (£6.58 for 2 years) rather than any significant clinical improvement in knee pain.

Whilst a monetary value was not attached to the opportunity cost of time spent exercising, the importance of the individual burden incurred by exercise therapy should not be ignored. The majority of subjects reported spending 10 to 20 minutes on the exercises, an average of 5 to 7 times per week. Lack of time or motivation was cited as a major reason for failure to continue with the exercise programme and it is therefore an important factor in determining the efficacy of the programme. Of those subjects who continued to exercise throughout the 24-month period, the majority reported having built the exercise programme into their daily routine. This included performing the exercises alongside existing routines (e.g. after bathing), or whilst performing other activities (e.g. watching television).

Provision of the study interventions did not result in a change in either total medical costs or primary care costs during the period of the study. However, the wide variability of the economic data and low power of the study meant that findings were difficult to interpret.

Of possibly greater significance is the importance of personnel costs in determining the overall cost of the programme. It is not within the remit of this study to make policy decisions regarding the wider implementation of exercise therapy. Nevertheless, it is noteworthy that this programme was implemented quickly and safely as a home-based exercise programme by non-specialist staff. Whilst better eligibility screening by a trained physiotherapist may result in improved outcomes, implementation and subsequent follow-up could be

conducted by physiotherapy assistants or district nurses. This may be especially true for follow-up visits, when the primary focus would be on general advice and encouragement. It is equally true that treatment sessions could be delivered from GP surgeries or hospitals, rather than as home visits. In effect this would transfer the time and expense of travel from the health provider to the patient. Whether or not this would impact on treatment adherence is impossible to tell from the current study.

The cost implications of continued treatment adherence are of interest. The degree to which patients adhere to the programme has implications for both costs and consequences. In sensitivity analysis, the additional costs incurred by a fully compliant population were compensated for by the fact that the NNT was correspondingly lower (NNT = 6 versus 9). However, given the intensive nature of exercise therapy, improved adherence with the programme is unlikely to be achieved with ease.

Presentation of the patient-specific cost-effectiveness data as an 'acceptability curve' allows policy decision-makers to assess their willingness to implement the programme assuming a variety of ceiling limits. Data from the trial suggested that there was an 80% probability that the exercise programme would be cost-effective (compared to normal care), with an investment of £500 per unit of effect. Given the high prevalence of self-reported knee pain in the community, this could represent a substantial burden. Further work may be

necessary in order to assess those patients most likely to benefit from the programme.

4.4.2 Comparison with other studies

Economic evaluation of exercise therapy is still relatively rare. None of the efficacy studies discussed to date included concurrent economic analysis. Full economic evaluation includes consideration of all costs and consequences resulting from a given intervention. However, given the paucity of data in relation to exercise therapy for knee OA, comparison of current findings with average published treatment costs is possibly more informative. The 2-year exercise programme implemented by this study incurred direct treatment costs of £112 per person (1996 £ sterling). A course of hospital-based physiotherapy typically cost £150 per person in the same year (Netten and Dennett, 1996). Whilst little has been reported on the relative efficacy of hospital physiotherapy compared to home-based exercise, two studies have reported that the observed improvements were comparable (Green et al. 1993; Chamberlain et al. 1982). More importantly, the exercise programme assessed in the current study represented treatment costs over a 2-year period. By comparison, hospital physiotherapy is generally short-term in nature, with very little long-term follow-up. As previously discussed, adherence with an exercise programme generally diminishes once regular contact is withdrawn (Sullivan et al. 1998; Chamberlain et al. 1982). As a result, the direct costs of the current

intervention (which resulted in continued exercise adherence in approximately 40% of subjects) is low compared to hospital care.

One study to have reported a change in medical costs resulting from exercise therapy compared individual home exercise and group exercise therapy for the treatment of ankylosing spondylitis (Bakker et al. 1994). Medical costs were reduced for both treatment groups over the 9-month treatment period, (individual exercise by 35% and group therapy by 44%). However, baseline costs were based on self-completion questionnaires requiring recall of medical resource use during the preceding year. Any assessment of baseline costs may therefore have been subject to recall bias. Since the study included no control group, it was not possible to quantify this effect. In addition, cost-effectiveness analysis was based only on those subjects who completed a 'cost diary' throughout the 9-month period. This represented 77% of the initial sample and may have introduced further bias.

The cost-effectiveness of social support has been more widely addressed. Weinberger et al. (1993) presented cost-effectiveness data relating to the provision of regular telephone support to patients with osteoarthritis. This study reported telephone support to be highly cost-effective, although no change in medical costs was observed. It is noteworthy that the direct treatment costs for the study were extremely low ($14.88 per patient per year). This was lower than figures reported by the current study; largely because of the dramatically different personnel costs ($6 per hour versus £18 per hour).

Direct comparison is difficult as the costing year was not explicitly stated in the Weinberger study.

A further study to examine the impact of social support on health care resource use reported reduced medical costs compared to a no-intervention control group (Cronan et al. 1997a). This significant result represented a remarkable increase in health care costs for the control group of almost 100% in year one and of 112% in year 2 (n =86). These dramatic increases were explained by differences in the number of days in hospital between the control and the intervention groups (the mean number of days for the control group increased from 0.05 to 1.15, whilst the mean for the experimental group increased from 0.23 to 0.55). Caution should be used in interpreting such cost data, since they are based on very high cost but low frequency events. In addition, it is important to note that social support consisted of weekly group meetings designed to promote empathy and the sharing of coping techniques. This was clearly very different to the social support provided through the telephone intervention of the current study.

A more widely investigated programme is that of the Arthritis Self-Management Programme (ASMP). This is a broad cognitive-behavioural programme that seeks to effect behavioural change. Several studies have reported this programme to be cost-effective (Kruger et al. 1998; Barlow et al. 1997; Lorig et al. 1993b). It is reported to reduce health care costs; with possible reductions in physician visits by as much as 40% (Lorig et al. 1993b).

However, these studies usually report relatively high service use at baseline (average of 8 to 9 GP visits per year for patients with OA). This is higher than rates found in the current study, where the average number of GP visits for the 6-month baseline period was 2.2 (arthritis related visits accounted for only 0.5 visits per person). Whilst different study populations could partially account for such differences, it is also likely that the conflicting results reflect the very different health care system available in the USA.

The potential impact of the ASMP in a UK population was examined by Barlow et al. (1998). This study reported similar baseline resource use to that observed in the Lorig investigation (GP visits over the baseline 4-month period were 2.7 per person – equivalent to 8.1 visits per year). However, almost 50% of the UK sample had a GP diagnosis of RA; for whom medical costs are known to be high. In addition, short-term reductions in GP consultations were observed at 6 months, but these were not maintained at 12 months. The investigators pointed to the impact of free health care at point of delivery to explain the possible disparity between American and UK findings.

A second UK based study examined the cost-effectiveness of a nurse-led education programme for the treatment of knee OA, delivered as 4 group sessions at local GP surgeries (Lord et al. 1999). Outcomes were assessed at 12 months and revealed no significant differences between the intervention and control groups in health outcomes. The incremental cost of delivering the education programme was £239 per person (1996 £ sterling) and no difference

was observed between the intervention and control group in health service resource use. The investigators concluded that their education programme was not a cost-effective use of healthcare resources.

4.4.3 Strengths and weaknesses of the study

This economic analysis was conducted alongside a large-scale RCT and was able to address important issues relating to the implementation of future community-based interventions. Drummond, (1995) identified the fundamental criterion for the inclusion of economic analysis alongside a clinical trial as being the quality of the trial itself. He suggested that:

> *"the strongest candidates for concurrent economic analysis are those trials with random allocation of participants to experimental and control groups, with blinded assessment of outcomes on an intent-to-treat basis and with sufficient sample size to detect the predetermined clinically important differences at the conventional levels of statistical significance"* (Drummond, 1995), p1403.

Whilst the current study was able to fulfil these criteria, the level of power required for the clinical outcome was insufficient for the detection of differences in cost data. Similar difficulties have been reported previously (Gray et al. 1997), although it is possible that the resources required in order achieve adequate power for economic evaluation will always be beyond the scope of a RCT.

The demographics of the study population were also important. Baltussen et al. (1996) pointed to the potential difficulties of extrapolating clinical findings from young study populations, and the possible impact of this on cost-effectiveness ratios. The age distribution of subjects within the current study reflected the age distribution of those most commonly affected by knee OA and should therefore have been representative of the target population.

In July 1994 the second Conference on Outcome Measures in RA Clinical Trials (OMERACT) accepted that rheumatology was falling behind other disciplines in the use of quality-of-life and utility scales (Tugwell, 1996). They recommended the adoption of utility scales as a matter of urgency in all aspects of rheumatological research. Quality-of-life was measured within the current study, although the EuroQol EQ-5D proved an insensitive tool within this context. Other researchers have reported similar difficulties when using the EuroQol for patients with knee OA (Fransen and Edmonds, 1999).

Whilst every effort was made to follow the available guidelines for the implementation of economic evaluation (Jefferson et al. 1996), some degree of bias and uncertainty necessarily remains. One of the strengths of the current trial was that details of health care costs were obtained from medical notes, rather than through self-completion questionnaires. This meant that interpretation of results was not limited by missing data and recall bias. However, errors may have been incorporated into the dataset as a result of illegible GP handwriting, poor communication between secondary and primary

care and recorder error. Nevertheless, researchers were blind to treatment group during case note abstraction. Any uncertainty should therefore have effected all treatment groups equally.

5 Summary and conclusion

5.1 Main findings

This thesis describes a series of inter-related studies designed to examine: i) the prevalence of knee pain in a community-based sample; ii) the efficacy of providing a home-based exercise programme to a sub-sample of this population; iii) the estimated cost of knee pain, and iv) the cost-effectiveness of providing the exercise therapy. Prevalence was assessed using a postal questionnaire, which was sent to all patient aged ≥45 years from two participating general practices in the Nottingham area. Treatment interventions were assessed through a pragmatic, factorial, randomised controlled trial of two-year duration. Cost data were collected prospectively alongside the clinical trial and analysis assumed a societal perspective.

The postal questionnaire was returned by 65% of the study population. The prevalence of self-reported knee pain in the community based on returned questionnaires was 32% (21% of the total population). These rates are similar to those observed by others (O'Reilly et al. 1998; McAlindon et al. 1992).

The intervention study was unique in that it was a large pragmatic study, designed to examine the long-term impact of a simple home-exercise programme in the community. Primary outcomes were assessed at 24 months and attempts were made to control for the psychosocial aspects of treatment provision and placebo effects.

Results of the intervention study showed modest improvements in self-reported knee pain, physical function and knee stiffness at 24 months for volunteers allocated to the exercise intervention. These effects were incremental to normal care. The telephone support and dolomite control groups did not show significant improvements at 24 months. Assessment of treatment adherence suggested that 40% of those allocated to the exercise programme continued to perform the exercises after 2 years. Adherence at this rate was achieved by providing a single review visit every 6 months (following the initial training period of 4 visits). This represented considerably less input from health professionals than had been used in previous studies reporting similar levels of treatment adherence (van Baar et al. 1998b; Ettinger et al. 1997). Volunteers most likely to continue with the programme were those who had built the exercises into their existing daily routine. Regression analysis suggested that volunteers with high baseline pain scores and those allocated to the exercise programme were most likely to show improvements in knee pain at 24 months. Low muscle strength, obesity, anxiety, bilateral pain and radiographic OA were all associated with poorer outcomes.

The cost-of-illness study suggested that costs to the health provider for the treatment of knee pain in the community were modest (mean £37 per annum). Knee costs were approximately 10% of the total direct medical costs. However, exact figures were difficult to ascertain as the isolation of knee-specific costs was often problematic. It is of note that only 29% of the study

sample consulted their GP for knee-related care during the 6-month study period. Despite a predominantly retired study population, indirect costs were high. Sensitivity analysis suggested that the inclusion of indirect costs resulted in a 75% increase from £38,762 per annum to £66,032 per annum in societal costs attributed to knee pain.

Economic analysis of the trial interventions was conducted prospectively alongside the RCT. Direct intervention costs for the exercise programme were £113 per person for the 24-month treatment period. No differences were observed between the treatment groups in medical or societal costs. Cost-effectiveness analysis based on direct treatment costs suggested that the incremental cost-effectiveness of achieving a ≥50% improvement in a single individual at 24 months was £1,012. An indication of the variability of the patient-specific cost data (including direct treatment cost, medical costs and personal costs) was presented as an acceptability curve. This suggested that exercise therapy had an 80% probability of being cost-effective if the health provider and patient were prepared to pay £500 per unit of effect on the WOMAC pain scale. Given the high prevalence of knee pain in the community, this could represent a substantial burden. Further work may be necessary in order to assess those patients most likely to benefit from the programme.

5.2 Interpretation

Knee pain is common in men and women aged over 45 years, and inflicts a sizeable physical, psychosocial and economic burden. The provision of a simple home exercise programme as outlined in this thesis could help to alleviate some of the pain and disability associated with knee pain, although such improvements are likely to be modest. It is unlikely that the cost of delivering the exercise programme would be ameliorated by fewer health contacts or reduced medication costs, and given the high prevalence of knee pain, the cost of delivering this programme could be substantial.

5.3 Recommendations for the future

This study aimed to demonstrate that subjects with knee pain could benefit from exercise therapy regardless of a clinical diagnosis of OA. Evidence was provided to suggest that patients most likely to benefit from the intervention were those with moderate levels of knee pain, poor muscle strength and who were not overweight. Further work to identify possible predictors of response that could be used by general practitioners in prescribing exercise therapy would help to improve the efficacy of the treatment. Secondly, the importance of continued treatment participation is consistently reported. An improved understanding of how to encourage greater individual responsibility for the management of chronic pain would be useful.

Frequency of resource use data from the trial suggested that drug therapy was important in the medical management of knee pain. By contrast physiotherapy or advice to lose weight were rarely documented. The current study was not designed as a formal audit of current practice. Nevertheless, the recent publication of updated guidelines for the medical management of knee OA Pendleton, Arden, et al. (2000) means that such an audit would now be informative. In addition, more research into alternative treatments such as the use of health food products, aromatherapy and osteopathy would be helpful in elucidating the personal cost of knee pain more accurately.

Finally, every effort was made to adhere to the published guidelines for conducting economic evaluations alongside clinical trials. Nevertheless, controversy continues over the most appropriate methods to be used for the collection, analysis and dissemination of the results of economic analyses (Johnston et al. 1999, pg 38). Until these issues are resolved, the comparability of study findings and generalisability of results will continue to be problematic.

References

ACR subcommittee on osteoarthritis guidelines (2000) Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis & Rheumatism* **43**, 1905-1915.

Adams, M.E., McCall, N.T., Gray, D.T., Orza, M.J. and Chalmers, T.C. (1992) Economic analysis in randomized control trials. *Medical Care* **30**, 231-239.

Altman, D.G. (1998) Confidence intervals for the number needed to treat. *BMJ* **317**, 1309-1312.

Altman, R.D. (1991) Classification of disease: osteoarthritis. *Seminars in Arthritis and Rheumatism* **20**, 40-47.

Altman, R.D. (1995) The classification of osteoarthritis. *Journal of Rheumatology* **22**, 42-43.

Altman, R.D., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., *et al.* (1986a) Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. *Arthritis and Rheumatism* **29**, 1039-1049.

Altman, R.D., Fries, J. and Bloch, D. (1986b) Radiographic assessment of progression of osteoarthritis. *Arthritis and Rheumatism* **29**, 1039-1049.

Altman, R.D., Fries, J., Bloch, D., Carstens, J., Cooke, T.D., Genant, H., et al. (1987) Radiographic assessment of progression in osteoarthritis. *Arthritis and Rheumatism* **30**, 1214-1225.

Altman, R.D., Hochberg, M.C., Murphy, W.A. and Wolfe, F. (1995) Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis and Cartilage* **3**, 3-70.

Andersson, H.I., Ejlertsson, G., Leden, I. and Schersten, B. (1999) Impact of chronic pain on health care seeking, self care, and medication. Results from a population-based Swedish study. *Journal of Epidemiology and Community Health* **53**, 503-509.

Badley, E.M. (1995b) The economic burden of musculoskeletal disorders in Canada (is similar to that for cancer, and may be higher). *Journal of Rheumatology* **22**, 204-206.

Badley, E.M. (1995a) The effect of osteoarthritis on disability and health care use in Canada. *Journal of Rheumatology* **22**, 19-22.

Badley, E.M., Rasooly, I. and Webster, G.K. (1994) Relative importance of musculoskeletal disorders as a cause of chronic health problems, disability, and health care utilization: findings from the 1990 Ontario Health Survey. *Journal of Rheumatology* **21**, 505-514.

Bagge, E., Bjelle, A., Eden, S. and Svanborg, A. (1991) Factors associated with radiographic osteoarthritis: results from the population study 70-year-old people in Goteborg. *Journal of Rheumatology* **18**, 1218-1222.

Bagge, E., Bjelle, A. and Svanborg, A. (1992) Radiographic osteoarthritis in the elderly. A cohort comparison and a longitudinal study of the "70-year old people in Goteborg". *Clinical Rheumatology* **11**, 486-491.

Bakker, C., Hidding, A., van der Linden, S. and van Doorslaer, E. (1994) Cost effectiveness of group physical therapy compared to individualized therapy for

ankylosing spondylitis. A randomised controlled trial. *Journal of Rheumatology* **21**, 264-268.

Baltussen, R., Leidl, R. and Ament, A. (1996) The impact of age on cost-effectiveness ratios and its control in decision making. *Health Economics* **5**, 227-239.

Barber, J.A. and Thompson, S.G. (1998) Analysis and interpretation of cost data in randomised controlled trials: review of published studies. *BMJ* **317**, 1195-1200.

Barlow, J. H., Turner, A. P., and Wright, E. A. (1998) Long-term outcomes of an arthritis self-management programme. *British Journal of Rheumatology*, 1315-1319.

Barlow, J.H., Williams, R.B. and Wright, C. (1997) Improving arthritis self-management in older adults: "Just what the doctor didn't order". *British Journal of Health Psychology* **2**, 175-185.

Bellamy, N. (1989) Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. *Seminars in Arthritis and Rheumatism* **18**, 14-17.

Bellamy, N. (1995) Instruments to assess osteoarthritis - current status and future needs. *Annals of the Rheumatic Diseases* **54**, 692-693.

Bellamy, N., Sothern, R.B. and Campbell, J. (1990) Rhythmic variation in pain perception in osteoarthritis of the knee. *Journal of Rheumatology* **17**, 364-372.

Bird, J.H. and Dixon, J.S. (1987) Measurement of pain. *Clinical Rheumatology* **1**, 71-89.

Blalock, S.J., DeVellis, B.M. and Giorgino, K.B. (1995) The relationship between coping and psychological well-being among people with osteoarthritis: a problem-specific approach. *Annals of Behavioural Medicine* **17**, 107-115.

Boegard, T., Rudling, O., Petersson, I.F. and Jonsson, K. (1998) Correlation between radiographically diagnosed osteophytes and magnetic resonance detected cartilage defects in the tibiofemoral joint. *Annals of Rheumatic Diseases* **57**, 401-407.

Boston, K., Pearce, S.A. and Richardson, P.H. (1990) The Pain Cognition Questionnaire. *Journal of Psychosomatic Research* **34**, 103-109.

Brandt, K. (1997) Putting some muscle into osteoarthritis. *Archives of Internal Medicine* **127**, 154-156.

Briggs, A. (2000) Economic evaluation and clinical trials: size matters. *BMJ* **321**, 1362-1363.

Briggs, A. and Fenn, P. (1998) Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. *Health Economics* **8**, 723-740.

Briggs, A. and Sculper, M. (1995) Sensitivity analysis in economic evaluation: a review of published studies. *Health Economics* **4**, 355-371.

Briggs, A., Sculper, M. and Buxton, M. (1994) Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Economics* **3**, 95-104.

Briggs, A., Wonderling, D. and Mooney, C. (1997) Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Economics* **6**, 327-340.

Britten, N., Stevenson, F.A., Barry, C.A., Barber, N. and Bradley, C.P. (2000) Misunderstandings in prescribing decisions in general practice: qualitative study. *BMJ* **320**, 484-488.

Brown, G.K. and Nicassio, P.M. (1987) Development of a questionnaire for the assessment of active and passive coping strategies in chronic pain patients. *Pain* **31**, 53-64.

Buckland-Wright, C. (1997) Current status of imaging procedures in the diagnosis, prognosis and monitoring of osteoarthritis. *Bailliere's Clinical Rheumatolgy* **11**, 727-748.

Burnett, S., Hart, D.J., Cooper, C. and Spector, T.D. (1994) *A radiographic atlas of osteoarthritis.*, London: Springer Verlag.

Chamberlain, M. A., Care, G., and Harfield, B. 91982) Physiotherapy in osteoarthrosis of the knees. A controlled trial of hospital versus home exercise. *International Rehab Medicine* **4(2)**, 101-106.

Chang, R.W., Pelliassier, J.M. and Hazen, G.B. (1996) A cost-effectiveness analysis of total hip arthroplasty for osteoarthritis of the hip. *JAMA* **275**, 858-865.

Chaudhary, M.A. and Stearns, S.C. (1996) Estimating confidence intervals for cost-effectiveness ratios: an example from a randomized trial. *Statistics in Medicine* **15**, 1447-1458.

Cicuttini, F.M., Baker, J., Hart, D.J. and Spector, T.D. (1996) Association of pain with radiological changes in different compartments and views of the knee joint. *Osteoarthritis and Cartilage* **4**, 143-147.

Claessans, A.A., Schouten, J.S., van den Ouweland, F.A. and Valkenburg, H.A. (1990) Do clinical findings associate with radiographic osteoarthritis of the knee? *Annals of the Rheumatic Diseases* **49**, 771-774.

Clark, A.G., Jordan, J.M., Vilim, V., Renner, J.B., Dragomir, A.D., Luta, G. and Kraus, V.B. (1999) Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity: the Johnston County Osteoarthritis Project. *Arthritis & Rheumatism* **42**, 2356-2364.

Clark, N.M. and Gong, M. (2000) Management of chronic disease by practitioners and patients: are we teaching the wrong things? *BMJ* **320**, 572-575.

Cook, R.J. and Sackett, D.L. (1995) The number needed to treat: a clinically useful measure of treatment effect. *BMJ* **310**, 452-454.

Cooper, C. (1995) Occupational activity and the risk of osteoarthritis. *Journal of Rheumatology* **22**, 10-12.

Cooper, C., Cushnaghan, J., Kirwan, J. and et al. (1992) Radiological assessment of the knee joint in osteoarthritis. *Annals of the Rheumatic Diseases* **51**, 80-82.

Cooper, C., McAlindon, T.E., Snow, S., Vines, K., Young, P., Kirwan, J. and Dieppe, P.A. (1994) Mechanical and constitutional risk factors for symptomatic knee osteoarthritis: differences between medial tibiofemoral and patellofemoral disease. *Journal of Rheumatology* **21**, 307-313.

Cooper, N.J. (2000) Economic burden of rheumatoid arthritis: a systematic review. *Rheumatology* **39**, 28-33.

Creamer, P. and Hochberg, M.C. (1997) Why does osteoarthritis of the knee hurt - sometimes? *British Journal of Rheumatology* **36**, 726-727.

Creamer, P., Lethbridge-Cejku, M. and Hochberg, M.C. (1999) Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. *Journal of Rheumatology* **26**, 1785-1792.

Croft, P. (1990) Review of UK data on the rheumatic diseases - 3. Osteoarthritis. *British Journal of Rheumatology* **29**, 391-395.

Croft, P., Papageorgiou, A.C., Ferry, S., Thomas, E., Jayson, M.I. and Silman, A.J. (1995) Psychologic distress and low back pain. Evidence from a prospective study in the general population. *Spine* **20**, 2731-2737.

Cronan, T.A., Durkin, K.A., Groessl, E. and Tomita, M. (1997b) Health care costs for volunteers and non-volunteers in an intervention for people with osteoarthritis. *Arthritis Care & Research* **10**, 36-42.

Cronan, T.A., Groessl, E. and Kaplan, R.M. (1997a) The effects of social support and education interventions on health care costs. *Arthritis Care and Research* **10**, 99-110.

Davis, M.A., Ettinger, W.H. and Neuhaus, J.M. (1990) Obesity and osteoarthritis of the knee: evidence from the National Health and Nutrition Examination Survey (NHANES 1). *Seminars in Arthritis and Rheumatism* **20**, 34-41.

Davis, M.A., Ettinger, W.H., Neuhaus, J.M., Barclay, J.D. and Segal, M.R. (1992) Correlates of knee pain among US adults with and without radiographic knee osteoarthritis. *Journal of Rheumatology* **19**, 1943-1949.

Davis, M.A., Ettinger, W.H., Neuhaus, J.M. and Mallon, K.P. (1991) Knee osteoarthritis and physical functioning: evidence from the NHANES I Epidemiologic Followup Study. *Journal of Rheumatology* **18**, 591-598.

Dekker, J., Tola, P., Aufdemkampe, G. and Winckers, M. (1993) Negative affect, pain and disability in osteoarthritis patients: the mediating role of muscle weakness. *Behaviour Research Therapy* **31**, 203-206.

Dexter, P. and Brandt, K. (1994) Distribution and predictors of depressive symptoms in osteoarthritis. *Journal of Rheumatology* **21**, 279-286.

Deyle, G., Henderson, N., Matekel, R., Ryder, M., Garber, M., Allison, S. (2000) Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee: a randomized controlled trial. *Annals of Internal Medicine* **132**, 173-181.

Dieppe, P., Chard, J., Tallon, D. and Egger, M. (1999) Funding clinical research. *Lancet* **353**, 1626

Dieppe, P., Cushnaghan, J., Jasani, M.K., McCrae, F. and Watt, I. (1993) A two-year, placebo-controlled trial of non-steroidal anti-inflammatory therapy in osteoarthritis of the knee joint. *British Journal of Rheumatology* **32**, 595-600.

Dieppe, P. and Szebenyi, B. (2000) Evidence based rheumatology. *Journal of Rheumatology* **27**, 4-7.

Dieppe, P.A., Basler, H.-D., Chard, J., Croft, P., Dixon, J.S., Hurley, M.V., Lohmander, S. and Raspe, H. (1999) Knee replacement surgery for osteoarthritis: effectiveness, practice variations, indications and possible determinants of utilization. *Rheumatology* **38**, 73-83.

Doherty, M., Jones, A. and Cawston, T.E. (1997) Osteoarthritis. In: Maddison, P.J., Isenberg, D.A., Woo, P. and Glass, D.N., (Eds.) *Oxford Textbook of Rheumatology.*, 2nd edn. pp. 1515-1553. Oxford: Oxford Medical Publications.

Donovan, J. and Blake, D.R. (2000) Qualitative study of interpretation of reassurance among patients attending rheumatology clinics: "just a touch of arthritis, doctor?". *BMJ* **320**, 541-544.

Drummond, M. (1995) Economic analysis alongside clinical trials: problems and potential. *Journal of Rheumatology* **22**, 1403-1407.

Drummond, M.F., Ferraz, M.B. and Mason, J. (1995) Assessing the cost-effectiveness of NSAIDs: an international perspective. *Journal of Rheumatology* **22**, 1408-1411.

Drummond, M.F., Jefferson, T.O. and BMJ Economic Evaluation Working Party. (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* **313**, 275-283.

Drummond, M.F., O'Brien, B., Stoddart, G. and Torrance, G.W. (1997) *Methods for the economic evaluation of health care programmes.*, 2nd edn. New York: Oxford University Press.

Drummond, M.F., Torrance, G.W. and Mason, J. (1993) Cost-effectiveness league tables: more harm than good.? *Social Science & Medicine* **37**, 33-40.

Efron, B. and Tibshirani, R. (1993) *An introduction to the bootstrap.*, 1st edn. New York: Chapman and Hall.

Elixhauser, A. ed. (1993) Health care cost-benefit and cost-effectiveness analysis (CBA/CEA). From 1979 to 1990: a bibliography. *Medical Care* **31 (suppl)**, JS1-149.

Ettinger, W.H., Burns, R., Messier, S.P., Applegate, W., Rejeski, W.J., Morgan, T., *et al.* (1997) A randomized trial comparing aerobic exercise with a health education program in older adults with knee osteoarthritis. The fitness arthritis and seniors trial (FAST). *JAMA* **277**, 25-31.

EuroQol Group. (1990) EuroQol - A new facility for the measurement of health-related quality of life. *Health Policy* **16**, 199-208.

Felson, D.T. (1988) Epidemiology of hip and knee osteoarthritis. *Epidemiological Review* **20**, 2-28.

Felson, D.T. (1990) The epidemiology of knee osteoarthritis: results from the Framingham Osteoarthritis Study. *Seminars in Arthritis and Rheumatism* **20**, 42-50.

Felson, D.T. (1995) Weight and osteoarthritis. *Journal of Rheumatology* **22**, 7-9.

Felson, D.T., Naimark, A., Anderson, J., Kazis, L., Castelli, W. and Meenan, R.F. (1987) The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis and Rheumatism* **30**, 914-918.

Felson, D.T., Zhang, Y., Hannan, M., Naimark, A., Weissman, B., Aliabadi, P. and Levy, D. (1997) Risk factors for incident radiographic knee osteoarthrtis in the elderley. The Framingham Study. *Arthritis & Rheumatism* **40**, 728-733.

Ferraz, M.B., Maetzel, A. and Bombardier, C. (1997) A summary of economic evaluations published in the field of rheumatology and related disciplines. *Arthritis & Rheumatism* **40** , 1587-1593.

Fisher, N.M. and Pendergast, D.R. (1997) Reduced muscle function in patients with osteoarthritis. *Scandinavian Journal of Rehabilitation Medicine* **29**, 213-221.

Forsen, L., Meyer, H.E., Sogaard, A.J., Naess, S., Schei, B. and Edna, T. (1999) Mental distress and risk of hip fracture. Do broken hearts lead to broken bones? *Journal of Epidemiology and Community Health* **53**, 343-347.

Fransen, M. and Edmonds, J. (1999) Reliability and validity of the EuroQol in patients with osteoarthritis of the knee. *Rheumatology* **38**, 807-813.

Gabriel, S.E. (1995) Economic evaluation using mathematical models: the case of misoprostol prophylaxis. *Journal of Rheumatology* **22**, 1412-1414.

Gabriel, S.E., Crowson, C.S., Campion, M.E. and O'Fallon, W.M. (1997a) Direct medical costs unique to people with arthritis. *Journal of Rheumatology* **24**, 719-725.

Gabriel, S.E., Crowson, C.S., Campion, M.E. and O'Fallon, W.M. (1997b) Indirect and nonmedical costs among people with rheumatoid and osteoarthritis compared with nonarthritic controls. *Journal of Rheumatology* **24**, 43-48.

Gabriel, S.E., Crowson, C.S. and O'Fallon, W.M. (1995) Costs of osteoarthritis: estimates from a geographically defined population. *Journal of Rheumatology* **22**, 23-25.

Gabriel, S.E., Crowson, C.S. and O'Fallon, W.M. (1999) Comorbidity in arthritis. *Journal of Rheumatology* **26**, 2475-2479.

Garratt, A.M., Ruta, D.A., Abdalla, M.I., Buckingham, J.K. and Russell, I.T. (1993) The SF-36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *BMJ* **306**, 1440-1444.

Gecht, M.R., Connell, K.J., Sinacore, J.M. and Prohaska, T.R. (1996) A survey of exercise beliefs and exercise habits among people with arthritis. *Arthritis Care and Research* **9**, 82-88.

Gerard, K. and Mooney, G. (1993) QALY league tables: handle with care. *Health Economics* **2**, 59-64.

Gold, M.R., Siegel, J.E., Russell, L.B. and Weinstein, M.C. (1996) *Cost-effectiveness in health and medicine.*, New York: Oxford University Press.

Gray, A.M., Marshall, M., Lockwood, A. and Morris, J. (1997) Problems in conducting economic evaluations alongside clinical trials. *British Journal of Psychiatry* **170**, 47-52.

Green, J., McKenna, F., Redfern, E.J. and Chamberlain, M.A. (1993) Home exercises are as effective as outpatient hydrotherapy for osteoarthritis of the hip. *British Journal of Rheumatology* **32**, 812-815.

Griffiths, B., Emery, P. and Akehurst, R. (1995) Economic evaluation in rheumatology: a necessity for clinical studies. *Annals of Rheumatic Diseases* **54**, 863-864.

Gunther, K.P., Sturmer, T., Sauerland, S., Zeissig, I., Sun, Y., Kessler, S., Brenner, H. and Puhl, W. (1998) Prevalence of generalised osteoarthritis in patients with advanced hip and knee osteoarthritis: the Ulm Osteoarthritis Study. *Annals of the Rheumatic Diseases* **57**, 717-723.

Gunther, K.P. and Sun, Y. (1999) Reliability of radiographic assessment in hip and knee osteoarthritis. *Osteoarthritis & Cartilage* **7**, 239-246.

Hadler, N.M. (1992) Knee pain is the malady - not osteoarthritis. *Annals of Internal Medicine* **116**, 598-599.

Harding, A.E. (1929) An investigation into the cause of arthritic muscle atrophy. *Lancet* **1**, 433-434.

Hart, D.J., Doyle, D.V. and Spector, T.D. (1999) Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. *Arthritis & Rheumatism* **42**, 17-24.

Hart, D.J. and Spector, T.D. (1993) The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. *Journal of Rheumatology* **20**, 331-335.

Hart, D.J. and Spector, T.D. (1995) Radiographic criteria for epidemiologic studies of osteoarthritis. *Journal of Rheumatology* **22**, 46-48.

Healthcare Financial Management Association. Introductory guide to NHS finance in the UK. 4th ed., London: HFM; 1998.

Hillman, A.L. and Bloom, B.S. (1989) Economic effects of prophylactic use of misoprostol to prevent gastric ulcer in patients taking non-steroidal anti-inflammatory drugs. *Archives of Internal Medicine* **149**, 2061-2065.

Hochberg, M.C., Kasper, J., Williamson, J. and et al. (1995) The contribution of osteoarthritis to disability: preliminary data from the womens' health and aging study. *Journal of Rheumatology* **22 (Suppl.)**, 16-28.

Hochberg, M.C., Lawrence, R.C., Everett, D.F. and Cornoni-Huntley, J. (1989) Epidemiologic associations of pain in osteoarthritis of the knee: data from the

National Health and Nutrition Examination Survey and the National Health and Nutrition Examination-I Epidemiologic Follow-up Survey. *Seminars in Arthritis and Rheumatism* **18**, 4-9.

Hofman, A., Grobber, D.E., De Jong, P.V. and van den Ouweland, F.A. (1991) Determinants of disease and disability. *European Journal of Epidemiology* **7**, 403-422.

Hollis, S. and Campbell, F. (1999) What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* **319**, 670-674.

Holman, H.R. and Lorig, K.R. (1997) Patient education: essential to good health care for patients with chronic arthritis. *Arthritis & Rheumatism* **40**, 1371-1373.

Holman, H.R. and Lorig, K.R. (2000) Patients as partners in managing chronic disease. *BMJ* **320**, 526-527.

Holmes, T.H. and Rahe, R.H. (1967) The Social Readjustment Rating Scale. *Journal of Psychosomatic Research* **11**, 213-218.

Hopman-Rock, M., Odding, E., Hofman, A., Kraaimaat, F.W. and Bijlsma, J. (1996) Physical and psychosocial disability in elderly subjects in relation to pain in the hip and / or knee. *Journal of Rheumatology* **23**, 1037-1044.

Huijsman, R. (1995) Economic evaluation of care for chronically ill: a literature review. *European Journal of Public Health* **5**, 8-19.

Hutton, C.W. (1989) Osteoarthritis: The cause not result of joint failure. *Annals of Rheumatic Diseases* **48**, 958-961.

Ikai, M. and Steinhaus, A.H. (1961) Some factors modifying the expression of human strength. *Journal of Applied Physiology* **16**, 157-163.

Jacobsson, L.T.H. (1996) Definitions of osteoarthritis in the knee and hand. *Annals of Rheumatic Diseases* **55**, 656-658.

Jefferson, T.O., Demicheli, V. and Mugford, M. (1996) *Elementary economic evaluation in health care*, 1st edn. London: BMJ Publishing Group.

Jensen, G.M. and Lorish, C.D. (1994) Promoting patient cooperation with exercise programs: linking research, theory, and practice. *Arthritis Care & Research* **7**, 181-189.

Johnston, K., Buxton, M.J., Jones, D.R. and Fitzpatrick, R. (1999) Assessing the costs of healthcare technologies in clinical trials. *Health Technology Assessment* **3**, 1-76.

Jones, A.C. (1994) Assessment of muscle function in knee osteoarthritis. [Thesis]. University of Nottingham. MD.

Jones, A.C., Hopkinson, N., Pattrick, M., Berman, P. and Doherty, M. (1992) Evaluation of a method for clinically assessing osteoarthritis of the knee. *Annals of the Rheumatic Diseases* **51**, 243-245.

Jones, A.C., Ledingham, J., McAlindon, T., Regan, M., Hart, D., MacMillan, P.J. and Doherty, M. (1993) Radiographic assessment of patellofemoral osteoarthritis. *Annals of the Rheumatic Diseases* **52**, 655-658.

Jones, D.A. and Round, J.M. (1990) Anonymous *Skeletal muscle in health and disease. A textbook of muscle physiology*, pp. 102. Manchester: Manchester University Press.

Jordan, J., Luta, G., Renner, J., Dragomir, A., Hochberg, M. and Fryer, J. (1997) Knee pain and knee osteoarthritis severity in self-reported task specific disability: The Johnston County Osteoarthritis Project. *Journal of Rheumatology* **24**, 1344-1350.

Jordan, J., Luta, G., Renner, J., Linder, G.F., Dragomir, A., Hochberg, M.C. and Fryer, J. (1996) Self-reported functional status in osteoarthritis of the knee in a rural southern community: The role of sociodemographic factors, obesity and knee pain. *Arthritis Care and Research* **9**, 273-278.

Jurmain, R.D. and Kilgore, L. (1995) Skeletal evidence of osteoarthritis: a palaeopathological perspective. *Annals of the Rheumatic Diseases* **54**, 443-450.

Kahn, H. and Sempos, C. (1989) Statistical methods in Epidemiology. In: *Statistical methods in Epidemiology*, 1st edn. pp. 76-79. New York: Oxford University Press.

Katz, B.P. and Yelin, E.H. (1993) Prevalence and correlates of depressive symptoms among persons with rheumatoid arthritis. *Journal of Rheumatology* **20**, 790-796.

Kellgren, J.H. and Lawrence, J.S. (1957) Radiologic assessment of osteoarthritis. *Annals of the Rheumatic Diseases* **16**, 494-502.

Kovar, P.A., Allegrante, J.P., MacKenzie, C.R., Peterson, M.G.E., Gutin, B. and Charlson, M.E. (1992) Supervised fitness walking in patients with osteoarthritis of the knee. *Annals of Internal Medicine* **116**, 529-534.

Kramer, J.S., Yelin, E.H. and Epstein, W.V. (1983) Social and economic impacts of four musculoskeletal conditions. A study using national community-based data. *Arthritis & Rheumatism* **26**, 901-907.

Kruger, J.M.S., Helmick, C.G., Callahan, L.F. and Haddix, A.C. (1998) Cost-effectiveness of the arthritis self-help course. *Archives of Internal Medicine* **158**, 1245-1249.

Lanes, S.F., Lanza, L.L., Radensky, P.W., Yood, R.A., Meenan, R.F., Walker, A.M. and Dreyer, N.A. (1997) Resource utilization and cost of care for rheumatoid arthritis and osteoarthritis in a managed care setting: the importance of drug and surgery costs. *Arthritis & Rheumatism* **40**, 1475-1481.

Langley, P.C. (1995) Cost-effectiveness profiles with an expanding treatment population. *Clinical Therapeutics* **17**, 1207-1212.

Lanyon, P., Jones, A.C. and Doherty, M. (1996) Assessing progression of patellofemoral osteoarthritis: a comparison between two radiographic methods. *Annals of the Rheumatic Diseases* **55**, 875-879.

Laupacis, A., Feeny, D., Detsky, A.S. and Tugwell, P. (1992) How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. Special article. *Canadian Medical Association Journal* **146**, 473-481.

Laupacis, A., Sackett, D.L. and Roberts, R.S. (1988) An assessment of clinically useful measures of the consequences of treatment. Special article. *New England Journal of Medicine* **318**, 1728-1733.

Lawrence, J.S., Bremner, J.M. and Bier, F. (1966) Osteoarthrosis. Prevalence in the population and relationship between symptoms and X-ray changes. *Annals of Rheumatic Diseases* **25**, 1-23.

Lawrence, R.C., Hochberg, M.C., Kelsey, J.L. and et al. (1989) Estimates of the prevalence of selected arthritic and musculoskeletal diseases in the United States. *Journal of Rheumatology* **16**, 427-441.

Ledingham, J., Regan, M., Jones, A.C. and Doherty, M. (1993) Radiographic patterns and associations of osteoarthritis of the knee in patients referred to hospital. *Annals of the Rheumatic Diseases* **52**, 520-526.

Lethbridge-Cejku, M., Scott, W.W., Reichle, R., Ettinger, W.H., Zonderman, A., Costa, P., Tobin, J.D. and Hochberg, M.C. (1995) Association of radiographic features of osteoarthritis of the knee with knee pain: data from the Baltimore Longitudinal Study of Aging. *Arthritis Care and Research* **8**, 182-188.

Liang, M.H., Cullen, K.E., Larson, M., Thompson, M., Schwartz, J.A., Fossel, W.N., Roberts, W.N. and Sledge, C.B. (1986) Cost-effectiveness of total joint arthroplasty in osteoarthritis. *Arthritis and Rheumatism* **29**, 937-943.

Liang, M.H., Larson, M., Thompson, M., Eaton, H., McNamara, E., Katz, R. and Taylor, J. (1984) Costs and outcomes in rheumatoid arthritis and osteoarthritis. *Arthritis and Rheumatism* **27**, 522-529.

Lichtenberg, P.A., Skehan, N.W. and Swensen, C.H. (1998) The role of personality, recent life stress and arthritic severity in predicting pain. *Journal of Psychosomatic Research* **28**, 231-236.

Linet, M.S., Harlow, S.D., McLaughlin, J.K. and McCaffrey, L.D. (1989) A comparison of interview data and medical records for previous medical conditions and surgery. *Journal of Clinical Epidemiology* **42**, 1207-1213.

Lipscomb, J., Ancukiewicz, M., Parmigiani, G., Samsa, G., Matchar, D. and Hasselblad, V. (1998) Predicting the cost of illness: A comparison of alternative models applied to stroke. *Medical Decision Making* **18**, S39-S56

Lohmander, L.S. and Felson, D.T. (1997) Defining the role of molecular markers to monitor disease, intervention, and cartilage breakdown in osteoarthritis. *Journal of Rheumatology* **24**, 782-785.

Lord, J., Victor, C., Littlejohns, P., Ross, F. and Axford, J. (1999) Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee. *Health Technology Assessment* **3**, 1-55.

Lorig, K.R., Chastain, R.L., Ung, E., Shoor, S. and Holman, H.R. (1989b) Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. *Arthritis & Rheumatism* **32**, 37-44.

Lorig, K.R., Laurin, J. and Holman, H.R. (1984) Arthritis self-management: a study of the effectiveness of patient education for the elderly. *The Gerontologist* **24**, 455-457.

Lorig, K.R., Lubeck, D., Kraines, R.G., Seleznick, M. and Holman, H.R. (1985) Outcomes of self-help education for patients with arthritis. *Arthritis & Rheumatism* **28**, 680-685.

Lorig, K.R., Lubeck, D., Kraines, R.G., Seleznick, M. and Holman, H.R. (1995) Outcomes of self-help education for patients with arthritis. *Arthritis and Rheumatism* **28**, 680-685.

Lorig, K.R., Mazonson, P.D. and Holman, H.R. (1993a) Evidence suggesting that health education for self-management in patients with chronic arthritis has sustained health benefits while reducing health care costs. *Arthritis and Rheumatism* **36**, 439-446.

Lorig, K.R., Mazonson, P.D. and Holman, H.R. (1993b) Evidence suggesting that health education for self-management in patients with chronic arthritis has

sustained health benefits while reducing health care costs. *Arthritis & Rheumatism* **36**, 439-446.

Lorig, K.R., Seleznick, M., Lubeck, D., Ung, E., Chastain, R.L. and Holman, H.R. (1989a) The beneficial outcomes of the arthritis self-management course are not adequately explained by behavior change. *Arthritis & Rheumatism* **32**, 91-95.

Lorig, K.R., Sobel, D.S., Stewart, A.L., Brown, B.W., Bandura, A., Ritter, P., (1999) Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization. *Medical Care* **37**, 5-14.

Lorish, C.D. and Boutaugh, M.L. (1997) Patient education in rheumatology. *Current Opinion in Rheumatology* **9**, 106-111.

Lothgren, M. and Zethraeus, N. (2000) Definition, interpretation and calculation of cost-effectiveness acceptability curves. *Health Economics* **7**, 623-630.

Maetzel, A., Ferraz, M.B. and Bombardier, C. (1998) A review of cost-effectiveness analyses in rheumatology and related disciplines. *Current Opinion in Rheumatology* **10**, 136-140.

Magni, G., Moreschi, C., Rigatti-Luchini, S. and Merskey, H. (1994) Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. *Pain* **56** , 289-297.

Maisiak, R., Austin, J.S. and Heck, l. (1996) Health outcomes of two telephone interventions for patients with rheumatoid arthritis or osteoarthritis. *Arthritis and Rheumatism* **39**, 1391-1399.

Manne, S. and Zautra, A. (1992) Coping with arthritis. *Arthritis and Rheumatism* **35**, 1273-1280.

Manninen, P., Heliovaara, M., Rihimaki, H. and Makela, P. (1997) Does psychological distress predict disability? *International Journal of Epidemiology* **26**, 1063-1070.

Marks, R. (1993) Quadriceps strength training for osteoarthritis of the knee: a literature review. *Physiotherapy* **79**, 13-18.

Matthews, J.N.S. and Altman, D.G. (1996) Statistics notes: Interaction 2: compare effect sizes not P values. *BMJ* **313**, 808-809.

Matthews, J.N.S., Altman, D.G., Campbell, M.J. and Royston, P. (1990) Analysis of serial measurements in medical research. *BMJ* **300**, 230-235.

Maurer, B.T., Stern, A.G., Kinossian, B., Cook, K.D. and Schumacher, H.R., Jr. (1999) Osteoarthritis of the knee: isokinetic quadriceps exercise versus an educational intervention. *Archives of Physical Medicine & Rehabilitation* **80**, 1293-1299.

McAlindon, T.E., Cooper, C., Kirwan, J.R. and Dieppe, P.A. (1992) Knee pain and disability in the community. *British Journal of Rheumatology* **31**, 189-192.

McAlindon, T.E., Cooper, C., Kirwan, J.R. and Dieppe, P.A. (1993a) Determinants of disability in osteoarthritis of the knee. *Annals of Rheumatic Diseases* **52**, 258-262.

McAlindon, T.E. and Dieppe, P.A. (1989) OA: Definitions and Criteria. *Annals of the Rheumatic Diseases* **48**, 531-532.

McAlindon, T.E., Snow, S., Cooper, C. and Dieppe, P.A. (1993b) Radiographic patterns of knee osteoarthritis in the community: the importance of the patellofemoral joint. *Annals of the Rheumatic Diseases* **51**, 844-849.

McAlindon, T.E., Wilson, P.W., Aliabadi, P., Weissman, B. and Felson, D.T. (1999) Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham study. *American Journal of Medicine* **106**, 151-157.

McAuley, E., Lox, C. and Duncan, T.E. (1993) Long-term maintenance of exercise, self-efficacy and physiological change in older adults. *Journal of Gerontology* **48**, 218-224.

Menkes, C.J. (1991) Radiographic criteria for classification of osteoarthritis. *Journal of Rheumatology* **21**, 74-76.

Minor, M.A. (1996) Arthritis and exercise: the times they are a-changin'. *Arthritis Care and Research* **9**, 79-81.

Moffett, J.K., Bell-Syer, S., Llewlyn-Phillips, H., Farrin, A. and Barber, J. (1999) Randomised controlled trial of exercise for low back pain: clinical outcomes, costs, and preferences. *BMJ* **319**, 279-283.

Moore, R.A., Tramér, M.R., Carroll, D., Wiffen, P.J. and McQuay, H.J. (1998) Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ* **316**, 333-338.

Munro, J., Brazier, J., Davey, R. and Nicholl, J. (1997) Physical activity for the over-65s: could it be a cost-effective exercise for the NHS? *Journal of Public Health Medicine* **19**, 397-402.

Murphy, W.A. (1995) Updated osteoarthritis reference standard. *Journal of Rheumatology* **22**, 56-59.

Netten, A. and Dennett, J. (1996) *Unit costs of health and social care*, Canterbury: PSSRU.

Nicassio, P.M., Wallston, K.A., Callahan, L.F., Herbert, M. and Pincus, T. (1985) The measurement of helplessness in rheumatoid arthritis. The development of the Arthritis Helplessness Index. *Journal of Rheumatology* **12**, 462-467.

O'Brien, B., Drummond, M., Labelle, R. and Willan, A. (1994) In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. *Medical Care* **32**, 150-163.

O'Reilly, S. (1996) Knee pain and disability: a community study. [Thesis]. University of Nottingham. MD.

O'Reilly, S., Muir, K.R. and Doherty, M. (1998) Knee pain and disability in the Nottingham Community: association with poor health status and psychological distress. *British Journal of Rheumatology* **37**, 870-873.

O'Reilly, S., Muir, K.R. and Doherty, M. (1999) Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. *Annals of Rheumatic Diseases* **58**, 15-19.

O'Reilly, S.C., Jones, A.C., Muir, K.R. and Doherty, M. (1998) Quadriceps weakness in knee osteoarthritis: the effect on pain and disability. *Annals of the Rheumatic Diseases* **57**, 588-594.

O'Reilly, S.C., Muir, K.R. and Doherty, M. (1996) Screening for pain in knee osteoarthritis: which question? *Annals of the Rheumatic Diseases* **55**, 931-933.

Odding, E., Valkenburg, H.A., Algra, D., Vandenouweland, F.A., Grobber, D.E. and Hofman, A. (1998) Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam study. *Annals of Rheumatic Diseases* **57**, 203-208.

Oliveria, S.A., Felson, D.T., Cirillo, P.A., Reed, J.I. and Walker, A.M. (1999) Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. *Epidemiology* **10**, 161-166.

Paakkari, I. (1994) Epidemiological and financial aspects of the use of non-steroidal anti-inflammatory analgesics. *Pharmacology and Toxicology* **75**, 56-59.

Pendleton, A., Arden, N., Dougados, M., Doherty, M., Barnworth, B., Biiylsma, J.N.J. et al. (2000) EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Annals of Rheumatic Diseases* **59**, 944

Petersson, I. (1996) Occurrence of osteoarthritis of the peripheral joints in European populations. *Annals of Rheumatic Diseases* **55**, 659-664.

Pettiti, D.B. (1994) Advanced cost-effectiveness analysis. In: *Methods for quantitative synthesis in medicine.*, pp. 169-186. New York: Oxford University Press.

Radloff, L.S. (1977) The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement* **1**, 385-401.

Regan, C.A., Lorig, K.R. and Thoresen, C.E. (1988) Arthritis appraisal and ways of coping: Scale development. *Arthritis Care & Research* **1**, 139-150.

Rejeski, W.J., Ettinger, W.H., Martin, K. and Morgan, T. (1998) Treating disability in knee osteoarthritis with exercise therapy: a central role for self-efficacy and pain. *Arthritis Care & Research* **11**, 94-101.

Rene, J., Weinberger, M., Mazzuca, S.A., Brandt, K.D. and Katz, B.P. (1992) Reduction of joint pain in patients with knee osteoarthritis who have received monthly telephone calls from lay personnel and whose medical treatment regimens have remained stable. *Arthritis and Rheumatism* **35**, 511-515.

Rogers, J. and Dieppe, P.A. (1994) Is tibiofemoral osteoarthritis in the knee joint a new disease? *Annals of the Rheumatic Diseases* **53**, 612-613.

Rogers, J., Watt, I. and Dieppe, P.A. (1981) Arthritis in Saxon and mediaeval skeletons. *BMJ* **283**, 1668-1670.

Rothfuss, J., Mau, W., Zeidler, H. and Brenner, M.H. (1997) Socioeconomic evaluation of rheumatoid arthritis and osteoarthritis: a literature review. *Seminars in Arthritis and Rheumatism* **26**, 771-779.

Ruchlin, H.S., Elkin, E.B. and Paget, S.A. (1997) Assessing cost-effectiveness analyses in rheumatoid arthritis and osteoarthritis. *Arthritis Care and Research* **10**, 413-421.

Russell, L.B., Gold, M.R., Siegel, J.E., Daniels, N. and Weinstein, M.C. (1996) The role of cost-effectiveness analysis in health and medicine. *JAMA* **276**, 1172-1177.

Rutten-van Molken, M., van Doorslaer, E., Jansen, M., Kerstijens, H. and Rutten, F. (1995) Costs and effects of inhaled corticosteroids and bronchodilators in asthma and chronic obstructive pulmonary disease. *American Journal of Respiratory Critical Care Medicine* **151**, 975-982.

Rutten-van Molken, M., van Doorslaer, E. and van Vliet, R. (1994) Statistical analysis of cost outcomes in a randomized controlled trial. *Health Economics* **3**, 333-345.

Salaffi, F., Cavalieri, F., Nolli, M. and Ferraccioli, G. (1991) Analysis of disability in knee osteoarthritis. Relationship with age and psychological variables but not with radiographic score. *Journal of Rheumatology* **18**, 1581-1586.

Sandmark, H., Hogstedt, C., Lewold, S. and Vingard, E. (1999) Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy. *Annals of the Rheumatic Diseases* **58**, 151-155.

Schouten, J.S.A.G. and Valkenburg, H.A. (1995) Classification criteria: methodological considerations and results from a 12 year follow-up study in the general population. *Journal of Rheumatology* **22**, 44-45.

Semble, E.L., Loeser, R.F. and Wise, C.M. (1990) Therapeutic exercise for rheumatoid arthritis and osteoarthrtis. *Seminars in Arthritis and Rheumatism* **20**, 32-40.

Sharma, L. and Felson, D. (1998) Studying how osteoarthritis causes disability: nothing is simple. *Journal of Rheumatology* **25**, 1-4.

Sharma, L., Hayes, K.W., Felson, D.T., Buchanan, T.S., Kirwan-Mellis, G., Lou, C., Pai, YC and Dunlop, D.D. (1999) Does laxity alter the relationship between strength and physical function in knee osteoarthritis? *Arthritis & Rheumatism* **42**, 25-32.

Skevington, S.M. (1983) Chronic pain and depression: universal or personal helplessness? *Pain* **15**, 309-317.

Slemenda, C., Brandt, K.D., Heilmam, D.K., Mazzuca, S.A., Braunstein, E.M., Katz, B.P. and Wolinsky, F.D. (1997) Quadriceps weakness and osteoarthritis of the knee. *Annals of Internal Medicine* **127**, 97-104.

Slemenda, C., Heilman, D.K., Brandt, K.D., Katz, B.P., Mazzuca, S.A., Braunstein, E.M. and Byrd, D. (1998) Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? *Arthritis & Rheumatism* **41**, 1951-1959.

Spector, T.D., Harris, P.A., Hart, D.J., Cicuttini, F.M., Nandra, D., Etherington, et al. (1996) Risk of osteoarthritis associated with long-term weight-bearing sports: a radiologic survey of the hips and knees in female ex-athletes and population controls. *Arthritis and Rheumatism* **39**, 988-995.

Spector, T.D. and Hart, D.J. (1992) How serious is knee osteoarthritis? *Annals of the Rheumatic Diseases* **51**, 1105-1106.

Spector, T.D., Hart, D.J. and Leedham-Green, M. (1991) The prevalence of knee and hand osteoarthritis in the general population using different clinical criteria: the Chingford study. *Arthritis and Rheumatism* **34**, 171

Spector, T.D. and Hochberg, M.C. (1994) Methodological problems in the epidemiological study of osteoarthritis. *Annals of Rheumatic Diseases* **53**, 143-146.

Steffen, O., Lise, D. and Haheim, L.L. (1998) Psychosocial risk factors and mortality: A prospective study with special focus on social support, social participation, and locus of control in Norway. *Journal of Epidemiology and Community Health* **52**, 476-481.

Stein, M.J., Wallston, K.A., Nicassio, P.M. and Castner, N.M. (1988) Correlates of a clinical classification schema for the Arthritis Helplessness Subscale. *Arthritis & Rheumatism* **31**, 876-881.

Sullivan, T., Allegrante, J.P., Peterson, M.G.E., Kovar, P.A. and MacKenzie, C.R. (1998) One-year follow-up of patients with osteoarthritis of the knee who participated in a program of supervised fitness walking and supportive patient education. *Arthritis Care and Research* **11**, 228-233.

Summers, M.N., Haley, W.E., Reveille, J.D. and Alarcon, G.S. (1988) Radiographic assessment and psychologic variables as predictors of pain and functional impairment in osteoarthritis of the knee or hip. *Arthritis & Rheumatism* **31**, 204-209.

Superio-Cabuslay, E., Ward, M.M. and Lorig, K.R. (1996) Patient education interventions in osteoarthritis and rheumatoid arthritis: a meta-analytic comparison with nonsteroidal antiinflammatory drug treatment. *Arthritis Care and Research* **9**, 292-301.

Sutton, A., Muir, K.R. and Jones, A.C. (1997) Two knees or one person: data analysis strategies for paired joints or organs. *Annals of the Rheumatic Diseases* **56**, 410-402.

Tambour, M., Zethraeus, N. and Johannesson, M. (1998) A note on confidence intervals in cost-effectiveness analysis. *International Journal of Technology Assessment in Health Care* **14**, 467-471.

Thompson, S.G. and Barber, J. (2000) How should cost data in pragmatic randomised trials be analysed? *BMJ* **320**, 1197-1200.

Tobin, D.L., Holroyd, K.A., Reynolds, R.V. and Wigal, J.K. (1989) The hierarchical factor structure of the Coping Strategies Inventory. *Cognitive Therapy and Research* **13**, 343-361.

Tornvall, G. (1963) Assessment of physical capabilities with special reference to the evaluation of maximal voluntary isometric muscle strength and maximal working capacity. *Acta Physiologica Scandinavica* **58**, 1-102.

Tugwell, P. (1996) Economic evaluation of the management of pain in osteoarthritis. *Drugs* **52**, 48-58.

Udvarhelyi, S., Colditz, G.A. and Epstein, A.M. (1992) Cost-effectiveness and cost-benefit analyses in the medical literature. Are the methods being used correctly? *Annals of Internal Medicine* **116**, 238-244.

van Baar, M., Dekker, J., Lemmens, J.A.M., Oostendorp, R.A.B. and Bijlsma, J.W.J. (1998a) Pain and disability in patients with osteoarthritis of hip or knee: the relationship with articular, kinesiological, and psychological characteristics. *Journal of Rheumatology* **25**, 125-133.

van Baar, M., Dekker, J., Oostendorp, R.A.B., Bijl, D., Voorn, T.B., Lemmens, J.A.M. and Bijlsma, J. (1998b) The effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a randomized clinical trial. *Journal of Rheumatology* **25**, 2432-2439.

van Baar, M.E., Assendelft, W.J., Dekker, J., Oostendorp, R.A. and Bijlsma, J.W. (1999) Effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review of randomized clinical trials. [Review] *Arthritis & Rheumatism* **42**, 1361-1369.

van Hout, B., Gordon, G. and Rutten, F. (1994) Costs, effects and C/E-ratios alongside a clinical trial. *Health Economics* **3**, 309-319.

van Jaarsveld, C.H.M., Jacobs, J.W.G., Schrijvers, A.J.P., Heurkens, A.H.M., Haanen, H.C.M. and Bijlsma, J.W.J. (1998) Direct cost of rheumatoid arthritis during the first six years: a cost-of-illness study. *British Journal of Rheumatology* **37**, 837-847.

van Sasse, J.L., van Romunde, L.K., Cats, A., van den Broucke, J.P. and Valkenburg, H.A. (1989) Epidemiology of osteoarthritis in a Dutch population with that in 10 other populations. *Annals of the Rheumatic Diseases* **48**, 271-280.

van Tulder, M.W., Koes, B.W. and Bouter, L.M. (1995) A cost-of-illness study of back pain in the Netherlands. *Pain* **62**, 233-240.

Wallston, B.S., Alagna, S.W., DeVellis, B.M. and DeVellis, R.F. (1983) Social support and physical health. *Health Psychology* **2**, 367-391.

Weinberger, M., Hiner, S.L. and Tierney, W.M. (1986) Improving functional status in arthritis: the effect of social support. *Social Science & Medicine* **23**, 899-904.

Weinberger, M., Tierney, W.M. and Booher, P. (1990) Social support, stress and functional status in patients with osteoarthritis. *Social Science & Medicine* **30**, 503-508.

Weinberger, M., Tierney, W.M., Booher, P. and Katz, B.P. (1989) Can the provision of information to patients with osteoarthritis improve functional status? A randomized, controlled trial. *Arthritis & Rheumatism* **32**, 1577-1583.

Weinberger, M., Tierney, W.M., Cowper, P.A., Katz, B.P. and Booher, P. (1993) Cost-effectiveness of increased telephone contact for patients with osteoarthritis. A randomized controlled trial. *Arthritis & Rheumatism* **36**, 243-245.

Weinstein, M.C., Siegel, J.E., Gold, M.R., Kamlet, M.S. and Russell, L.B. (1996) Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* **276**, 1253-1258.

Wolfe, F. (1999) Determinants of WOMAC function, pain and stiffness scores: evidence for the role of low back pain, symptom counts, fatigue and depression in osteoarthritis, rheumatoid arthritis and fibromyalgia. *Rheumatology* **38**, 355-361.

Wolfe, F. and Hawley, D.J. (1997) Measurement of the quality of life in rheumatic disorders using the Euroqol. *British Journal of Rheumatology* **36**, 786-793.

Wood, P.H. (1976) Osteoarthritis in the community. *Clinical Rheumatic Disease* **2**, 495-507.

Woolf, A.D. and Doherty, M. (2000) Education to improve the health of the nation: Who should we educate? *Annals of Rheumatic Diseases* **59**, 401-403.

Xuan, J., Kirchdoerfer, L.J., Boyer, J.G. and Norwood, G.J. (1999) Effects of comorbidity on Health-Related Quality-of-Life scores: an analysis of clinical trial data. *Clinical Therapeutics* **21**, 383-403.

Yelin, E.H. and Callahan, L.F. (1995) The economic cost and social and psychological impact of musculoskeletal conditions. *Arthritis and Rheumatism* **38**, 1351-1362.

Young, A. (1993) Current issues in arthrogenous inhibition. *Annals of the Rheumatic Diseases* **52**, 829-834.

Ytterberg, S.R., Mahowald, M.L. and Krug, H.E. (1994) Exercise for arthritis. *Bailliere's Clinical Rheumatolgy* **8**, 161-189.

Zhang, Y., Glynn, R.J. and Felson, D.T. (1996) Musculoskeletal disease research: should we analyze the joint or the person? *Journal of Rheumatology* **23**, 1130-1134.

Zigmond, A.S. and Snaith, R.P. (1983) The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica* **67**, 361-370.

Appendices

Appendix 1: Consent forms

DEPARTMENT OF HEALTH, KNEE PAIN INTERVENTION STUDY

CONSENT FORM

A community-based, randomised intervention study examining the effects of exercise on knee pain and its associated disability.

(1) CLINICAL AND RADIOGRAPHIC ASSESSMENT

I voluntarily agree to participate in the above study. I understand that I will:

1. Be examined by a trained therapist with respect to knee and other joint diseases, and answer additional questionnaires relating to my health.
2. Be investigated for muscle strength using an especially constructed chair.
3. Go for knee X-rays to the City Hospital, Nottingham.

I also give consent for my medical records to be examined as necessary.

I understand that I may withdraw from this study at any time, without prejudicing my future medical care or treatment.

I confirm that I have read and understood the information sheet provided for this study and have had the opportunity to ask questions therefrom.

Name:

Date:

Investigator:

Date:

DEPARTMENT OF HEALTH, KNEE PAIN INTERVENTION STUDY

CONSENT FORM

A community-based, randomised intervention study examining the effects of exercise on knee pain and its associated disability.

(2) TREATMENT STUDY

I voluntarily agree to participate in the above study. I understand that I will be randomly allocated to receive one or more of the following treatment regimes:

- Specific leg muscle exercises.
- Regular telephone contact from the Rheumatology Unit.
- A health food product containing Calcium; which is thought to be beneficial for osteoarthritis.
- General advice concerning knee pain and its management.

I realise that the treatment study will continue for 2 years and that I will be assessed at 6 months, 12 months, 18 months and 24 months in the same way as before.

I understand that I may withdraw from this study at any time without prejudicing my future medical care or treatment.

I confirm that I have read and understood the information sheet provided for this study and have had the opportunity to ask any questions arising therefrom.

Name: **Date:**

Investigator: **Date:**

Appendix 2: Recruitment questionnaire

ARTHRITIS IN THE COMMUNITY

This questionnaire has been prepared by the Rheumatology Unit, City Hospital Nottingham and the Department of Public Health Medicine and Epidemiology, Queens Medical Centre.

We want to find out more about the extent of knee pain in the community, in order to find ways of improving the management and care of osteoarthritis. It is therefore of great importance that you help us by filling in this questionnaire. Even if you do not have **knee pain**, please fill it in, as we are still very interested in your responses. We think you will find the questionnaire interesting and it should only take about 15-20 minutes to complete.

Most of the questions require a tick in a box, for the others, clear instructions are given. Much thought has gone into the design of this questionnaire, we are aware a few questions may seem similar - this is intentional and necessary for our research, please fill in **all** of them to the best of your ability.

Please return it in the pre-paid envelope (no stamp required) as soon as possible to the Department of Public Health Medicine and Epidemiology, Queens Medical Centre, Nottingham.

Your answers are strictly confidential.

Please do not pass this questionnaire onto anyone else.

If you have any questions about this work please ring :

Anna Follows, Study Administrator on 0115 9691169 extension 45557.
or
Alex Sutton, Research Assistant on 0115 9249924 extension 42004.

Thank you for your assistance with this important area of research.

*A small number of you may, at a later date, be invited to participate in a further study (which would involve an examination and X-Rays of your knees). Even if you would not be willing to help us further **please** return this questionnaire.*

Funded by the Department of Health

SECTION 1 : ABOUT YOURSELF

1. What is your surname?
(Please also include your maiden name, if applicable, in brackets)

. . . . . .

2. What are your first names?

. . . . . .

3. What is your date of birth?

☐☐ day ☐☐ month ☐☐ year

4. What sex are you? *(Tick one box only)*

☐ male
☐ female

5. What is your marital status?

☐ married
☐ single
☐ divorced
☐ widowed
☐ separated

6. What is your height?

☐☐ ft ☐☐ ins **or** ☐☐☐ cms

7. What is your weight?

☐☐ st ☐☐ lbs **or** ☐☐☐ kgs

8. **Has your weight changed a lot over your adult life? - (other than when pregnant, if relevant).** *(Tick one box only)*

1 ☐ no

2 ☐ gradual increase

3 ☐ gradual decrease

4 ☐ changeable

9. **What is your ethnic origin?** *(Tick one box only)*

1 ☐ White

2 ☐ Afro Caribbean

3 ☐ SE Asia

4 ☐ Middle Eastern

5 ☐ Indian, Pakistani or Bangladeshi

6 ☐ Mixed, please specify . . . . . .

7 ☐ Other, please specify . . . . . .

SECTION 2 : ABOUT YOUR EMPLOYMENT

10. Please give details of your current or last job.

What was the job title?

. . . . . .

Please give approximate dates during which you did this job.

☐☐ month ☐☐ year to ☐☐ month ☐☐ year

or *(tick)* ☐ still employed in the job

Please give details of your job including what the organisation you worked for make or do

. . . . . .

. . . . . .

11. Please give details of the longest job that you have held in your life.

What was the job title?

. . . . . .

Please give approximate dates during which you did this job.

☐☐ month ☐☐ year to ☐☐ month ☐☐ year

Please give details of your job including what the organisation you worked for make or do.

. . . . . .

. . . . . .

12. Please give details of your spouse or partner's current or last job including the job title.

. . . . . .

SECTION 3 : ABOUT YOUR SMOKING HABITS

13. **Have you ever smoked regularly i.e. at least once a day for at least 3 months.** *(Tick one box)*

☐ yes

☐ no

If yes, are you a - *(Tick one box)*

☐ current smoker

☐ ex-smoker

Approximately how many did you or do you smoke?

☐ / day

How long ago did you start smoking?

☐☐ months or ☐☐ years

If an ex-smoker, how long ago did you stop?

☐☐ weeks or ☐☐ months or ☐☐ years

SECTION 4 : ABOUT ANY TABLETS YOU MAY TAKE

14. Do you currently take pain killers bought over the counter or prescribed by your GP? *(Tick one box)*

☐ never

☐ occasionally

☐ regularly

If you do take pain killers please state which ones

. . . . . .

. . . . . .

15. Do you currently take any other medication prescribed by your GP? *(Tick one box)*

☐ yes

☐ no

If yes, please give the name(s) below:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

16. Do you take any herbalist or health food shop remedies for your joints? *(Tick one box)*

☐ yes

☐ no

If yes, please give the name(s) below:

. . . . . .

. . . . . .

SECTION 5 : ABOUT ANY PAIN YOU MAY SUFFER

17. ABOUT <u>BACK</u> PAIN:

(a) **Have you <u>ever</u> had back pain on most days for at least a month?** *(Tick one box)*

☐ yes

☐ no

If so, have you experienced any back pain during the last year? *(Tick one box)*

☐ yes

☐ no

(b) **Have you had back pain on most days in the <u>last month</u>?** *(Tick one box)*

☐ yes

☐ no

(c) **Have you had back pain <u>within the last year</u> that occurred on most days for at least a month?** *(Tick one box)*

☐ yes

☐ no

If so, at what age did you first notice this type of back pain?

. . . . . years old.

(d) **Have you ever injured your back?** *(Tick one box)*

☐ yes, if yes at what age did this occur ?. . . . . years old, or date. . . . . .

☐ no

If yes, did this injury require medical/hospital treatment? ☐ yes ☐ no

What was the cause of this injury? . . . . . .

18. ABOUT HIP PAIN:

(a) Have you ever had pain in or around a hip on most days for at least a month? *(Tick one box)*

☐ yes

☐ no

If so, have you experienced any hip pain during the last year? *(Tick one box)*

☐ yes

☐ no

(b) Have you had hip pain on most days of the last month? *(Tick one box)*

☐ yes

☐ no

(c) Have you had hip pain within the last year that occurred on most days for a least a month? *(Tick one box)*

☐ yes

☐ no

If so, at what age did you first notice this type of hip pain?

. . . . . years old.

(d) Have you ever suffered from clicking hips? *(Tick one box)*

☐ yes, if yes at what age did this occur ?. . . . . years old, or date. . . . . .

☐ no

If yes,did this injury require medical/hospital treatment? ☐ yes ☐ no

What was the cause of the injury?. . . . . .

19. **ABOUT KNEE PAIN:**

(a) **Have you ever had pain in or around a knee on most days for at least a month?** *(Tick one box)*

☐ yes

☐ no

If so, have you experienced any knee pain during the last year? *(Tick one box)*

☐ yes

☐ no

(b) **Have you had knee pain on most days of the last month?** *(Tick one box)*

☐ yes

☐ no

(c) **Have you had pain within the last year in or around the knee that occurred on most days for at least a month?** *(Tick one box)*

☐ yes

☐ no

If so, at what age did you first notice this type of knee pain?

. . . . . years old.

(d) **Have you ever injured either of your knees?** *(Tick one box)*

☐ yes, if yes at what age did this occur?. . . . . years old, or date. . . . . .

☐ no

If yes, did this injury require medical/hospital treatment? ☐ yes ☐ no

What was the cause of this injury?. . . . . .

SECTION 6 : ABOUT YOUR GENERAL HEALTH

20. Have you been diagnosed by your Doctor as having any of the following?
(Please tick any that apply)

1 ☐ Heart Disease
2 ☐ Stroke
3 ☐ Lung Disease
4 ☐ Cancer
5 ☐ Diabetes
6 ☐ Rheumatoid Arthritis
7 ☐ Osteoarthritis

21. In general, would you say your health is: *(tick one box)*

1 ☐ Excellent
2 ☐ Very good
3 ☐ Good
4 ☐ Fair
5 ☐ Poor

22. <u>Compared to one year ago,</u> how would you rate your general health <u>now</u>?
(tick one box)

1 ☐ Much better now than one year ago
2 ☐ Somewhat better now than one year ago
3 ☐ About the same
4 ☐ Somewhat worse now than one year ago
5 ☐ Much worse now than one year ago

SECTION 7 : HEALTH AND DAILY ACTIVITIES

23. **The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?**
(Please tick one box on each line)

	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
Lifting or carrying groceries	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐
Climbing one flight of stairs	☐	☐	☐
Bending, kneeling or stooping	☐	☐	☐
Walking more than a mile	☐	☐	☐
Walking half a mile	☐	☐	☐
Walking 100 yards	☐	☐	☐
Bathing and dressing yourself	☐	☐	☐

24. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**
(Please tick yes or no for each question)

Cut down on the amount of time you spent on work or other activities	☐ Yes	☐ No
Accomplished less than you would like	☐ Yes	☐ No
Were limited in the kind of work or other activities	☐ Yes	☐ No
Had difficulty performing the work or other activities (e.g. it took extra effort)	☐ Yes	☐ No

25. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems** (such as feeling depressed or anxious)? *(Please tick yes or no for each question)*

Cut down on the amount of time you spent on work or other activities	☐ Yes	☐ No
Accomplished less than you would like	☐ Yes	☐ No
Didn't do work or other activities as carefully as usual	☐ Yes	☐ No

26. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?** *(Please tick one)*

1 ☐ Not at all

2 ☐ Slightly

3 ☐ Moderately

4 ☐ Quite a bit

5 ☐ Extremely

27. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks?</u>** *(Please tick one)*

1 ☐ None

2 ☐ Very mild

3 ☐ Mild

4 ☐ Moderate

5 ☐ Severe

6 ☐ Very severe

28. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including work both outside the home and housework)?** *(Please tick one)*

1 ☐ Not at all

2 ☐ A little bit

3 ☐ Moderately

4 ☐ Quite a bit

5 ☐ Extremely

SECTION 8 : ABOUT YOUR FEELINGS

29. These questions are about how you feel and how things have been with you during the past month. (For each question, please indicate the one answer that comes closest to the way you have been feeling)
(Please tick one box on each line)

How much time during the past month:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Did you feel full of life?	☐	☐	☐	☐	☐	☐
Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
Did you feel worn out?	☐	☐	☐	☐	☐	☐
Have you been a happy person?	☐	☐	☐	☐	☐	☐
Did you feel tired?	☐	☐	☐	☐	☐	☐
Has your health limited your social activities (like visiting friends or close relatives)?	☐	☐	☐	☐	☐	☐

SECTION 9 : ABOUT YOUR HEALTH IN GENERAL

30. Please choose the answer that best describes how <u>true</u> or <u>false</u> each of the following statements is for you. *(Please tick one box on each line)*

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
I seem to get ill more easily than other people	☐	☐	☐	☐	☐
I am as healthy as anybody I know	☐	☐	☐	☐	☐
I expect my health to get worse	☐	☐	☐	☐	☐
My health is excellent	☐	☐	☐	☐	☐

We would like to ask you more about your health at the moment. For each question place a tick in the box that closest describes your health state.

31. Please indicate your level of mobility.

1 ☐ I have no problem in walking

2 ☐ I have some problems in walking about

3 ☐ I am confined to bed

32. Please indicate your level of self-care.

1 ☐ I have no problems with self-care

2 ☐ I have some problems washing or dressing myself

3 ☐ I am unable to wash or dress myself

33. Please indicate your ability to perform your usual activities.

1 ☐ I have no problems with performing my usual activities (eg. work, study, housework, family or leisure activities)

2 ☐ I have some problems with performing my usual activities

3 ☐ I am unable to perform my usual activities

34. Please indicate your level of pain.

1 ☐ I have no pain or discomfort

2 ☐ I have moderate pain or discomfort

3 ☐ I have extreme pain or discomfort

35. Please indicate your level of anxiety or depression.

1 ☐ I am not anxious or depressed

2 ☐ I am moderately anxious or depressed

3 ☐ I am extremely anxious or depressed

36. Compared with my general level of health over the past 12 months, my health state today is ...

1 ☐ Better

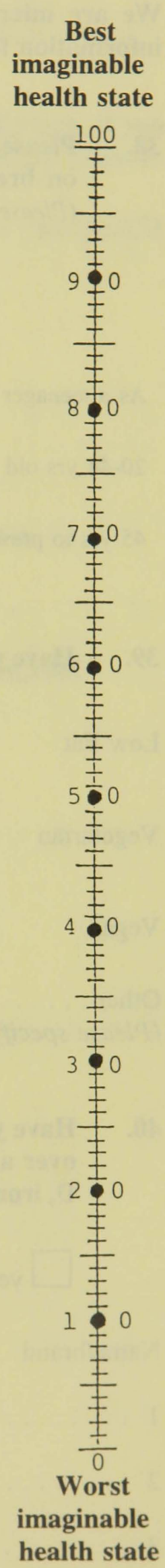
2 ☐ Much the same

3 ☐ Worse

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

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

Your own
health state today



SECTION 10 : ABOUT YOUR DIET

We are interested in certain key aspects of diet. Please try to recall the following information to the best of your ability.

38. Please indicate your total milk intake, including milky drinks, milk in drinks and on breakfast cereal etc. at different ages, by ticking the appropriate boxes.
(Please tick appropriate box)

	None	Up to ½ pt/week	More than ½ pt/week	Less than ½ pt/day	½ pt - 1 pt daily	More than 1 pt daily	Don't know
As a teenager	☐	☐	☐	☐	☐	☐	☐
20-44 yrs old	☐	☐	☐	☐	☐	☐	☐
45 yrs to present	☐	☐	☐	☐	☐	☐	☐

39. Have you *ever* followed any of the diets mentioned below? *(tick one box for each)*

Low Fat ☐ Yes ☐ No If yes Age : from . . . . . to . . . . . years

Vegetarian ☐ Yes ☐ No If yes Age : from . . . . . to . . . . . years

Vegan ☐ Yes ☐ No If yes Age : from . . . . . to . . . . . years

Other . . . . . Age : from . . . . . to . . . . . years
(Please specify)

40. Have you *ever* taken any vitamins, minerals or other food supplements regularly over a period of approximately six months or more (such as vitamin C, vitamin D, iron, calcium, fish oils, evening primrose oil, beta carotene etc.)? *(Tick one box)*

☐ yes ☐ no *(If yes, Please list brand, daily dose and age taken, if known)*

Name/brand	Daily Dose	Age taken
1	. . . . .	from . . . . . to . . . . . years
2	. . . . .	from . . . . . to . . . . . years
3	. . . . .	from . . . . . to . . . . . years
4	. . . . .	from . . . . . to . . . . . years

SECTION 11 : OCCUPATIONAL PHYSICAL ACTIVITY

We are interested in the decade of your life, between the ages of 40 and 50 years. If you are not yet 50 please consider the time period starting when you were 40 to the present.

The questions below ask about your habitual physical activity in the past i.e. please only answer for the time period defined.

41. Were you in full time employment?
(Please tick)

☐ yes, please name occupation . . . . . .

☐ no

If yes please answer the questions below before moving on to SECTION 12.
*If **no**, please go on to **SECTION 12 now (page no.20).***

*Questions 42-51 ask about the physical nature of your main occupation **at that time** **i.e. in your forties.***

Please put a ring around the responses which best described you then.

42. In your 40's, at work did you sit ...

never / seldom / sometimes / often / always

43. In your 40's, at work did you stand ...

never / seldom / sometimes / often / always

44. In your 40's, at work did you walk ...

never / seldom / sometimes / often / always

45. In your 40's, at work did you lift heavy loads ...

never / seldom / sometimes / often / very often

46. In your 40's, after work did you feel tired ...

very often / often / sometimes / seldom / never

47. In your 40's, at work through physical exertion did you used to sweat ...

very often / often / sometimes / seldom / never

48. In your 40's, do you think in comparison with others <u>at that age</u> your work was physically ...

much heavier / heavier / as heavy / lighter / much lighter

49. In your 40's, how many minutes did you walk per day to and from <u>work</u>? ...

. . . . . minutes.

50. In your 40's, how many minutes did you cycle per day to and from <u>work</u>? ...

. . . . . minutes.

51. In your 40's, what was your approximate weight?

☐☐ st ☐☐ lbs **or** ☐☐☐ kgs

SECTION 12 : LEISURE TIME PHYSICAL ACTIVITY

*While still thinking about the **same time in your life as previous section (i.e. in your forties)** please answer the following questions on leisure activities.*

52. Did you play any sports (e.g. golf, tennis, cricket etc), or participate in any physical activities (e.g. ballroom dancing, aerobics, hiking etc) ? ...

☐ yes

☐ no

If yes

- which sport did you play most frequently? . . . . . .
- how many hours a week? . . . . . hours
- how many months a year? . . . . . months

If you played a second sport:

- which sport is it? . . . . . .
- how many hours a week? . . . . . hours
- how many months a year? . . . . . months

Did you play any other sports ? - please list . . . . . .

. . . . . .

. . . . . .

For questions 53-61 please put a ring around the responses which best described you then.

53. Do you think in comparison with others your own age at that time, your physical activity during leisure time was ...

much more / more / the same / less / much less

54. During your leisure time did your activities cause you to sweat ...

very often / often / sometimes / seldom / never

55. During your leisure time did you play sport ...

never / seldom / sometimes / often / very often

56. During your leisure time did you watch television ...

never / seldom / sometimes / often / very often

57. During your leisure time did you walk ...

never / seldom / sometimes / often / very often

58. During your leisure time did you cycle ...

never / seldom / sometimes / often / very often

59. During your leisure time did you do DIY activities (e.g. home improvement, painting, etc)? ...

never / seldom / sometimes / often / very often

60. During your leisure time did you work in the garden ...

never / seldom / sometimes / often / very often

61. How many hours per day did you sleep on average?

. . . . . hours.

Appendix 3: Assessment questionnaire

REF NO □□□□□·□

Department of Health Knee Pain Study

ASSESSMENT:

NAME.....

DATE.....

NEXT ASSESSMENT.....

GROUP .....

X-RAY RECEIVED .....

If found please phone Louise Cooke on tel: (0115) 9691169 ext 45557.

REF NO☐☐☐☐☐☐

PATIENT SERVICE USE QUESTIONNAIRE

PERSONAL DETAILS

We would like you to complete the following questions about yourself.

1. What is your current employment situation?
(please tick appropriate box)

1☐ Full time employed

2☐ Part time employed

3☐ Retired

4☐ Unemployed

5☐ Not employed

2. Has your employment situation changed in the last 12 months?
(please tick appropriate box)

☐ No *(If ticked, please go straight to Q4)*

☐ Yes

3. Was the change due to knee pain?
(please tick appropriate box)

☐ No *(If ticked, please go straight to Q4)*

☐ Yes

If **Yes**, please state how your employment situation has been changed
(please tick appropriate box)

1☐ Stopped working

2☐ Reduced hours worked

3☐ Increased hours worked

4☐ Gone back to work

5☐ Other *(please explain)*

4. Have you taken any time off work in the last 6 months because of your knee pain?
(please tick appropriate box)

☐ No *(if no please go straight to Q6)*

☐ Yes *(if yes please answer Q5(a) and 5(b) before moving on to Q6)*

5. (a) Approximately how much time have you taken off work?

. . . . . hours/days/weeks *(delete as appropriate)*

5. (b) Was this time off work paid or unpaid? *(please tick appropriate box)*

1 ☐ Unpaid

2 ☐ Paid at full rate

3 ☐ Paid at reduced rate *(please explain)* . . . . . .

. . . . . .

. . . . . .

4 ☐ Do not know

6. Are covered by private health insurance? *(please tick appropriate box)*

☐ No

☐ Yes *(please explain briefly)*

. . . . . .

. . . . . .

7. Are you exempt from prescription charges? *(please tick appropriate box)*

☐ No

☐ Yes

We would like you to complete the following questions about your use of health services in the last six months. (For some services we ask about your use of them in the last year).

GENERAL PRACTICE

8. In the last 6 months have you seen your G.P in the surgery or at home? *(Please tick appropriate box)*

☐ No *(if no please go to Q10)*

☐ Yes

9. Were any of the times you were seen by the GP due partly or fully to your knee pain?

☐ No

☐ Yes

☐ Don't know

OUTPATIENTS

10. In the last 6 months have you attended a hospital outpatient clinic for consultation?

☐ No *(if no please go straight to Q12)*

☐ Yes *(if yes please list the hospitals you have attended as an outpatient)*

.....

.....

.....

11. Were any of the times you attended as an outpatient due partly or fully to your knee pain?

☐ No

☐ Yes

☐ Don't know

INPATIENT CARE

12. In the last **12** months have you been admitted to hospital for planned or emergency care?

☐ No *(if no please go straight to Q14)*

☐ Yes *if yes please list the hospitals you were admitted to:*

.....

.....

.....

13. Were any of the times you were admitted to hospital due partly or fully to your knee pain?

☐ No

☐ Yes

☐ Don't know

MEDICATION

We would like you to complete the following questions about your medication taken in the last six months.

14. In the last 6 months because of your knee pain have you been prescribed or purchased any tablets, medicine or creams or gels for your knee pain? *(please tick the appropriate box)*

☐ No *(if no please go straight to Q15)*

☐ Yes *(if yes please complete the following chart before moving on to Q15)*

Name of Medication	Prescribed by GP or hospital? (if yes please indicate which)	If not on prescription how many times did you purchase it?	What was the approximate cost of each purchase?

EQUIPMENT AND OTHER EXPENDITURES

We would like you to complete the following questions about any equipment bought to help your knee pain.

15. Do you have any equipment or items that you have obtained especially because of your knee pain? *(please tick appropriate box)*

☐ No *(if no please go straight to Q16)*

☐ Yes *(if yes please complete the following chart before moving to Q16)*

Please complete one row for each item or equipment.

Type of Equipment/ item	Did you purchase it? Yes/No	If provided by someone else, who was this?	Was this item purchased in the last 12 months? Yes/No	If known, what was the approximate cost?

16. In the last **12** months have you incurred any other further costs because of your knee pain? *(please tick appropriate box)*

☐ No

☐ Yes *(if yes please complete the following chart)*

Type of additional expenditure	What was the approximate extra cost?(please specify if one-off cost or regular amount)

PAST MEDICAL HISTORY

We would like to ask you about any operations or injuries you have had to your legs (including your knees, hips and back) which have lead you to hospitalisation.

Please list below the name of the operations or injuries you have had to your legs (or a brief description of what you had done in hospital), which hospital you attended and approximate dates.

operation / injury	hospital attended	date
1.	.....	.....
2.	.....	.....
3.	.....	.....
4.	.....	.....
5.	.....	.....

ABOUT YOUR HEALTH IN GENERAL

We would like to ask you more about your health at the moment. For each question please place a tick in the box that closest describes your health state.

1. Please indicate your level of mobility.

- ☐ I have no problem in walking
- ☐ I have some problems in walking about
- ☐ I am confined to bed

2. Please indicate your level of self-care.

- ☐ I have no problem with self-care
- ☐ I have some problem with washing or dressing myself
- ☐ I am unable to wash or dress myself

3. Please indicate your ability to perform your usual activities.

- ☐ I have no problems with performing my usual activities (e.g. work, study, housework, family or leisure activities)
- ☐ I have some problem with performing my usual activities
- ☐ I am unable to perform my usual activities

4. Please indicate your level of pain.

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

5. Please indicate your level of anxiety or depression.

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

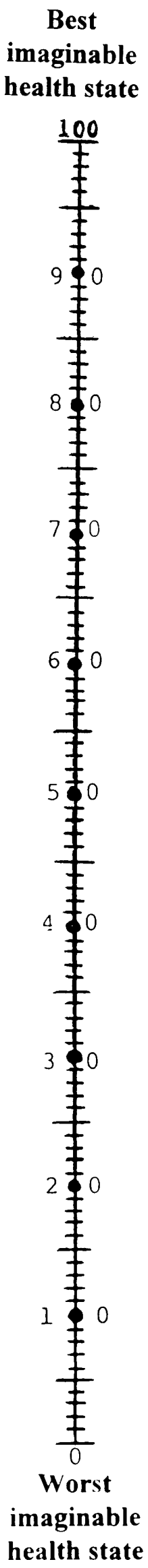
6. Compared with my general level of health over the past 12 months, my health state today is...

- ☐ Better
- ☐ Much the same
- ☐ Worse

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

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

Your own health state today



SF-36

SECTION 1: *ABOUT YOUR GENERAL HEALTH*

1. In general, would you say your health is: *(tick one box)*

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

2. <u>Compared to one year ago</u>, how would you rate your general health <u>now</u>? *(tick one box)*

- ☐ Much better now than one year ago
- ☐ Somewhat better now than one year ago
- ☐ About the same
- ☐ Somewhat worse now than one year ago
- ☐ Much worse now than one year ago

SECTION 2: *HEALTH AND DAILY ACTIVITIES*

3. **The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?** *(please tick one box on each line)*

	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigerous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
Lifting or carrying groceries	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐
Climbing one flight of stairs	☐	☐	☐
Bending, kneeling or stooping	☐	☐	☐
Walking more than a mile	☐	☐	☐
Walking half a mile	☐	☐	☐
Walking 100 yards	☐	☐	☐
Bathing and dressing yourself	☐	☐	☐

4. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?** *(please tick yes or no for each question)*

	Yes	No
Cut down on the amount of time spent on work or other activities	☐	☐
Accomplished less than you would like	☐	☐
Were limited in the kind of work or other activities	☐	☐
Had difficulty performing the work or other activities (e.g. it took extra effort)	☐	☐

5. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems** (such as feeling depressed or anxious)? *(please tick yes or no for each question)*

	Yes	No
Cut down on the amount of time you spent on work or other activities	☐	☐
Accomplished less than you would like	☐	☐
Didn't do work or other activities as carefully as usual	☐	☐

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?** *(Please tick one)*

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?** *(please tick one)*

- ☐ None
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including work both outside the home and housework)?** *(please tick one)*

- ☐ Not at all
- ☐ A little bit
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

SECTION 3 *ABOUT YOUR FEELINGS*

9. These questions are about how you feel and how things have been with you during the past month. (For each question, please indicate the one answer that comes closest to the way you have been feeling)
(please tick one box on each line)

How much time during the past month:	All of the time	Most of the time	A good bit of time	Some of the time	A little of the time	None of the time
Did you feel full of life?	☐	☐	☐	☐	☐	☐
Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
Did you feel worn out?	☐	☐	☐	☐	☐	☐
Have you been a happy person?	☐	☐	☐	☐	☐	☐
Did you feel tired?	☐	☐	☐	☐	☐	☐
Has your health limited your social activities (like visiting friends or close relatives)?	☐	☐	☐	☐	☐	☐

SECTION 4: *ABOUT YOUR HEALTH IN GENERAL*

10. Please choose the answer that best describes how <u>true</u> or <u>false</u> each of the following statements is for you. *(Please tick one box on each line)*

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
I seem to get ill more easily than other people	☐	☐	☐	☐	☐
I am as healthy as anybody I know	☐	☐	☐	☐	☐
I expect my health to get worse	☐	☐	☐	☐	☐
My health is excellent	☐	☐	☐	☐	☐

HAD INDEX

ABOUT YOUR GENERAL FEELINGS

For each item please tick one box

1. I feel tense or "wound up":

- ☐ Most of the time
- ☐ A lot of the time
- ☐ Time to time, occasionally
- ☐ Not at all

2. I still enjoy the things I used to enjoy:

- ☐ Definitely as much
- ☐ Not quite as much
- ☐ Only a little
- ☐ Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen:

- ☐ Very definitely and quite badly
- ☐ Yes, but not too badly
- ☐ A little, but it doesn't worry me
- ☐ Not at all

4. I can laugh and see the funny side of things:

- ☐ As much as I always could
- ☐ Not quite so much now
- ☐ Definitely not so much now
- ☐ Not at all

5. Worrying thoughts go through my mind:

- ☐ A great deal of the time
- ☐ A lot of the time
- ☐ From time to time but not too often
- ☐ Only occasionally

6. I feel cheerful:

- ☐ Not at all
- ☐ Not often
- ☐ Sometimes
- ☐ Most of the time

I can sit and feel relaxed:

- ☐ Definitely
- ☐ Usually
- ☐ Not often
- ☐ Not at all

I feel as if I am slowed down

- ☐ Nearly all the time
- ☐ Very often
- ☐ Sometimes
- ☐ Not at all

I get a sort of frightened feeling "like butterflies" in the stomach:

- ☐ Not at all
- ☐ Occasionally
- ☐ Quite often
- ☐ Very often

I have lost interest in my appearance:

- ☐ Definitely
- ☐ I don't take so much care as I should
- ☐ I may not take quite as much care
- ☐ I take just as much care as ever

11. I feel restless as if I have to be on the move:

- ☐ Very much indeed
- ☐ Quite a lot
- ☐ Not very much
- ☐ Not at all

12. I look forward with enjoyment to things:

- ☐ As much as I ever did
- ☐ Rather less than I used to
- ☐ Definitely less than I used to
- ☐ Hardly at all

13. I get sudden feelings of panic:

- ☐ Very often indeed
- ☐ Quite often
- ☐ Not very often
- ☐ Not at all

14. I can enjoy a good book or radio or TV programme:

- ☐ Often
- ☐ Sometimes
- ☐ Not often
- ☐ Very seldom

WOMAC OSTEOARTHRITIS INDEX

SECTION 1: PAIN

The following questions concern the amount of pain you have experienced in your knees over the last week. (*Please tick one box for each item).*

How much pain do you have?

		None	Mild	Moderate	Severe	Extreme
1.	Walking on a flat surface	☐	☐	☐	☐	☐
2.	Going up or down stairs	☐	☐	☐	☐	☐
3.	At night while in bed	☐	☐	☐	☐	☐
4.	Sitting or Lying	☐	☐	☐	☐	☐
5.	Standing Upright	☐	☐	☐	☐	☐

The following two questions are similar to those above but for these you indicate your response by putting an "X" on the horizontal line.

If you your "X" at the left hand of the line you are indicating that you have no pain.
If you put your "X" at the right hand end of the line you are indicating that your pain is extreme.

6. Walking on a flat surface

NO PAIN ——————————————————— EXTREME PAIN

7. Going up or down stairs

NO PAIN ——————————————————— EXTREME PAIN

SECTION 2: STIFFNESS

The following questions concern the amount of stiffness (not pain) you have experienced in your knees over the last week. Stiffness is a sensation of restriction or slowness in the ease with which you move your joints. *(Please tick one box for each item)*

8. How **severe** is your stiffness **after first wakening** in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

9. How **severe** is your stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SECTION 3: PHYSICAL FUNCTION

The following questions concern your physical function. By this we mean your ability to move around and look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced over the last week due to problems with your knees. *(Please tick one box for each item).*

What degree of difficulty do you have with:

	None	Mild	Moderate	Severe	Extreme
10. Descending stairs	☐	☐	☐	☐	☐
11. Ascending stairs	☐	☐	☐	☐	☐
12. Rising from sitting	☐	☐	☐	☐	☐
13. Standing	☐	☐	☐	☐	☐
14. Bending to floor	☐	☐	☐	☐	☐
15. Walking on the flat	☐	☐	☐	☐	☐
16. Getting in/out of car	☐	☐	☐	☐	☐

	None	Mild	Moderate	Severe	Extreme
17. Going shopping	☐	☐	☐	☐	☐
18. Putting on socks/stockings	☐	☐	☐	☐	☐
19. Rising from bed	☐	☐	☐	☐	☐
20. Taking off socks/stockings	☐	☐	☐	☐	☐
21. Lying in bed	☐	☐	☐	☐	☐
22. Getting in/out of bath	☐	☐	☐	☐	☐
23. Sitting	☐	☐	☐	☐	☐
24. Getting on/off toilet	☐	☐	☐	☐	☐
25. Heavy domestic duties	☐	☐	☐	☐	☐
26. Light domestic duties	☐	☐	☐	☐	☐

***NOW** we would like you to think again about each aforementioned symptoms which you have just rated.

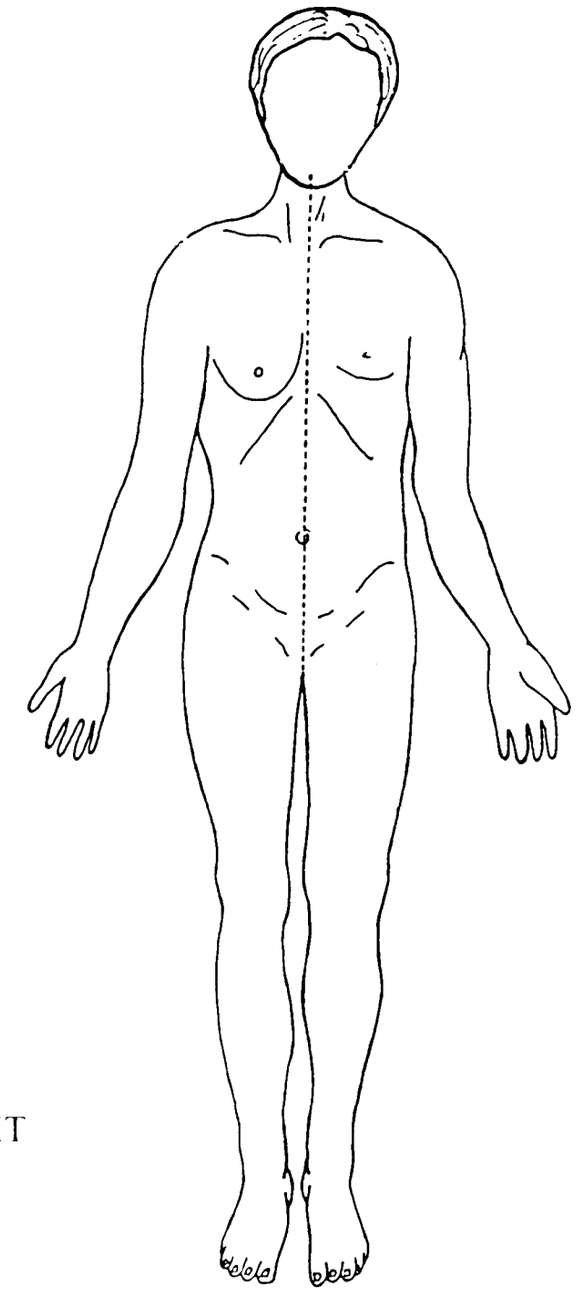
Then select **one** pain item (section 1), **one** stiffness item (section 2) and **one** physical function item (section 3) which are most important to you i.e. which you most hope could be **improved**.

Indicate your selections by circling the appropriate item numbers.

Remember to select only:
one pain item
and **one** stiffness item
and **one** physical function item

PAIN

Please shade on the diagram any areas where you normally suffer pain. Place a small "x" where the pain is most severe.



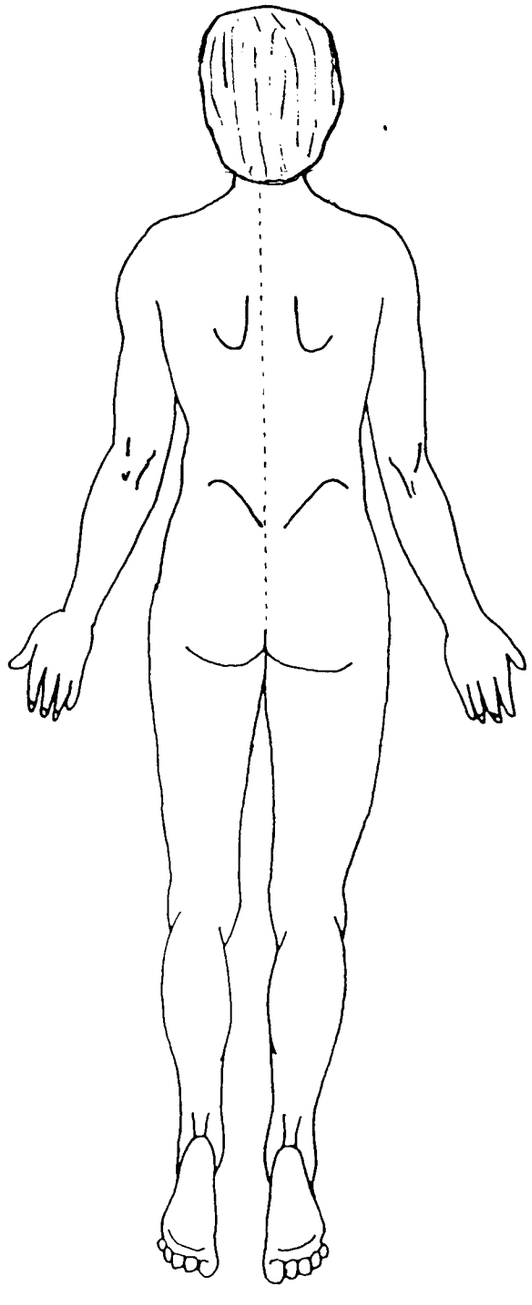
RIGHT LEFT

FRONT

Fibromyalgia Pain
(Axial & two diagonally opposite quadrants.
e.g. R arm & L leg)

1 = yes 0 = no

☐



LEFT RIGHT

BACK

REF NO ☐☐☐☐☐.☐

PHYSICAL EXAMINATION

HEIGHT ☐.☐☐ m WEIGHT ☐☐☐ kg

STANDING

1. **EXTENSION OF BACK** (pain)
   0=normal 1=abnormal ☐

   location of pain .....

2. **FLEXION OF BACK** (pain)
   0=normal 1=abnormal ☐

   location of pain .....

3. **HYPERMOBILITY SCREEN**

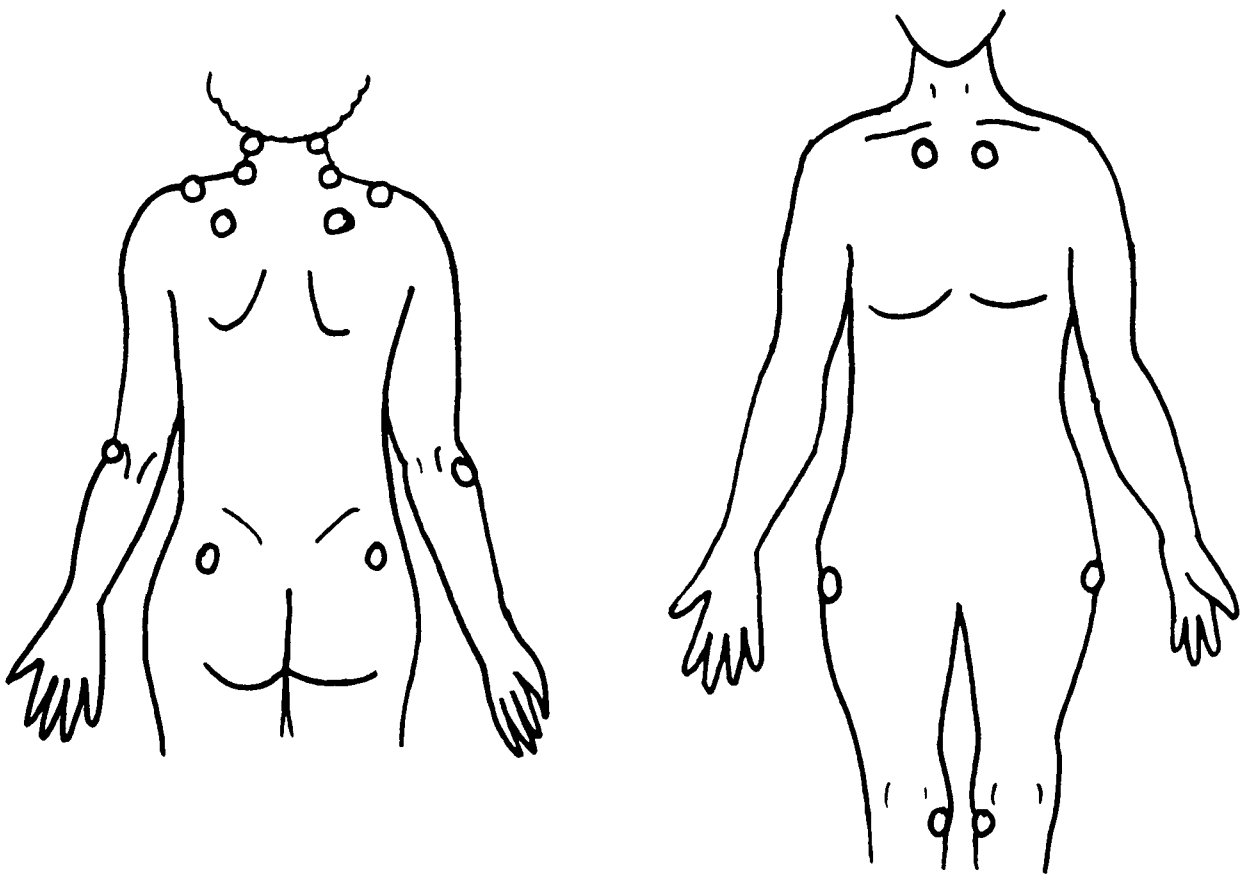
	0=normal 1=abnormal	Right	Left
a)	**Thumbs** (bring thumb back parallel to / touching forearm)	☐	☐
b)	**Little Fingers** (extend little finger >90°)	☐	☐
c)	**Elbows** (extend elbow >10°)	☐	☐
d)	**Knees** (extend knee >10°)	☐	☐
e)	**Touch Floor** (with both hands flat, legs straight)	☐	

maximum score=9 hypermobile=6 or more

TOTAL ☐

4. **FIBROMYALGIA SCREEN**

TENDER POINTS (tick if painful)



score 0-18 fibromyalgia=11 or more

(approximate force of 4kg) TOTAL ☐☐

ON THE COUCH

LYING FLAT

Right **Left**

1. **INTERNAL ROTATION OF HIPS** (pain or restriction of movement)

0=normal 1=abnormal ☐ ☐

location of pain **R**.....

L.....

2. **EXTERNAL ROTATION OF HIPS** (pain or restriction of movement)

0=normal 1=abnormal ☐ ☐

location of pain **R**.....

L.....

SITTING UP

			R	L
1.	**EFFUSION** 0=no or doubtful effusion 1=positive effusion 2=tense effusion		☐	☐
2.	**TEMPERATURE** 0=normal 1=warm		☐	☐
3.	**BONY SWELLING** 0=absent 1=present		☐	☐
4.	**CREPITUS** 0=absent 1=present		☐	☐
5.	**POPLITEAL CYST** 0=absent 1=present		☐	☐
6.	**JOINT LINE TENDERNESS**			
	0=no tenderness 2=subject winces	(a) Patellofemoral	☐	☐
	1=tender 3=subject withdraws	(b) Medial	☐	☐
		(c) Lateral	☐	☐
7.	**PERIARTICULAR TENDERNESS**			
	0=no tenderness 2=subject winces	(a) Inferomedial	☐	☐
	1=tender 3=subject withdraws	(b) Superomedial	☐	☐
		(c) Inferolateral	☐	☐
		(d) Superolateral	☐	☐
8.	**RANGE OF MOVEMENT** (passive / in degrees)			
	full extension		☐☐☐	☐☐☐
	full flexion		☐☐☐	☐☐☐
9.	**HEBERDENS NODES ON HANDS** 0-4 for each hand		☐	☐
10.	**THUMB IPJ NODES** 0=absent 1=present		☐	☐
11.	**THUMB BASE (squaring, crepitus, pain)** 0=normal 1=abnormal		☐	☐

Appendix 4: Information leaflet and general advice

- Twice weekly a single tablet of a health food product containing calcium, which is believed to be beneficial for osteoarthritis.

You will be seen again for re-assessment after 6 months, 1 year and 2 years. These will be the same as the first excluding the X-Rays which will only be repeated at the end of the 2 years.

Please Note: *You will be free to leave the study at any time without prejudicing the care or treatment that you might receive from your doctor or at the City Hospital. Your GP will know you are in the study but all the information that we obtain from you will be confidential.*

We appreciate this is a rather complex study and that it may involve your co-operation for a relatively long period (2 years). If there is anything you do not understand or wish to ask either now or later, please feel free to contact either **Louise Cooke (Research Therapist)** or **Anna Follows (Study Administrator)** **Tel: 0115 9691169 ext. 45557**

The name of the Therapist for your assessment is:

.....

WHO IS ORGANISING THE STUDY?

The study is co-ordinated by a team from the Rheumatology Unit (City Hospital) and the Department of Public Health Medicine and Epidemiology (University of Nottingham Medical School).

The study has been funded by the Department of Health and approved by the relevant ethics committees.

Steering Committee:

Professor Mike Doherty
(Consultant in Rheumatology)

Dr. Adrian Jones
(Consultant in Rheumatology)

Dr. Ken Muir
(Lecturer in Epidemiology)

Dr. Joan Bassey
(Senior Lecturer in Physiology)

Mr. Keith Tolley
(Health Economist)

Miss Louise Cooke
(Research Metrologist / Therapist)

Miss Kim Ratcliffe
(Research Metrologist / Therapist)

Mr. Alex Sutton
(Research Statistician)

Mrs. Anna Follows
(Study Administrator)

NOTTINGHAM City HOSPITAL

DEPARTMENT OF HEALTH

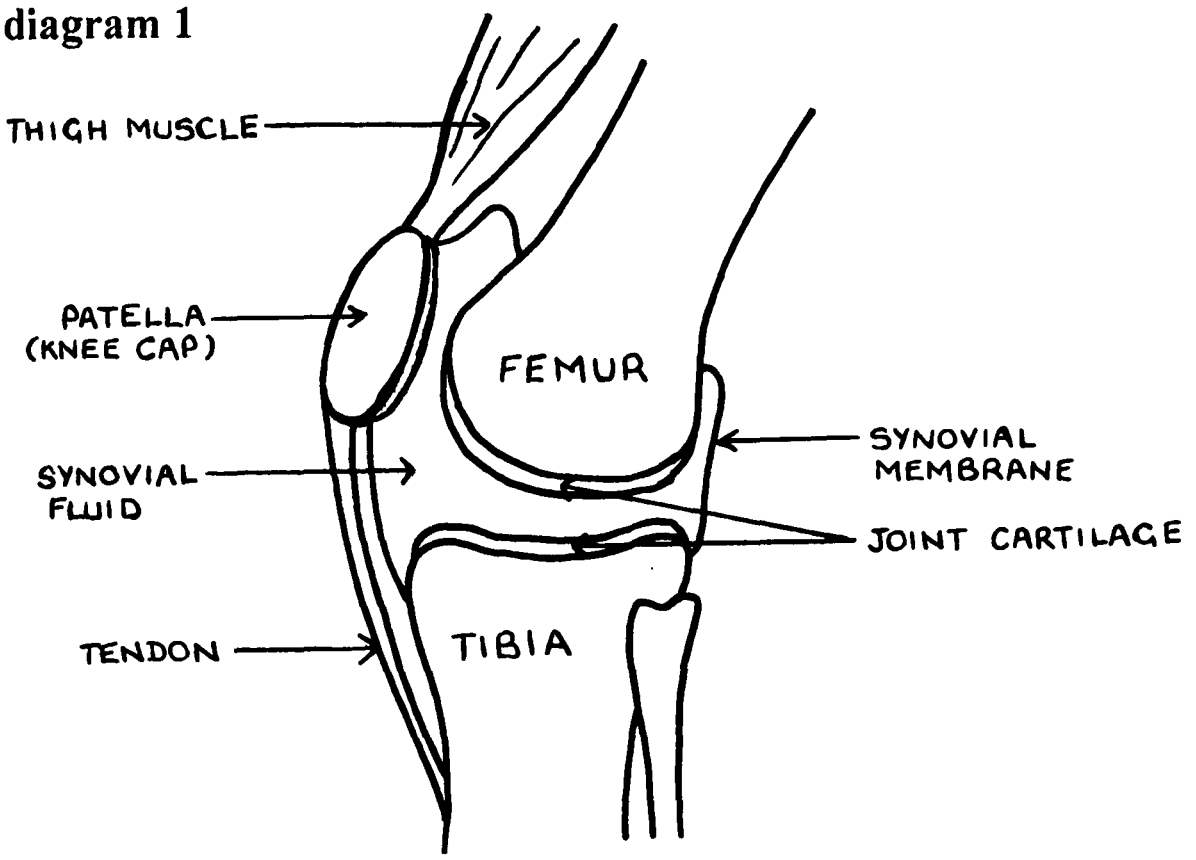
KNEE PAIN INTERVENTION STUDY

KNEE PAIN AND OSTEOARTHRITIS

Knee osteoarthritis is often a cause of knee pain and stiffness. It is a condition which becomes increasingly common among people over the age of 45 years. Osteoarthritis (OA) is a form of joint disease, which can make every day activities increasingly difficult to do.

In a normal knee joint the ends of our bone are covered by a thin layer of smooth gristle called cartilage. This acts as a shock absorber for the joint and it's smooth surface allows freedom of movement. The bone end and cartilage are surrounded by a membrane (synovial membrane) which produces a small amount of thick fluid (synovial fluid) to help oil these surfaces. These structures are enclosed in a protective capsule. The knee joint is stabilised by four ligaments (two inside and two outside the joint) which help prevent dislocation and the thigh muscles (quadriceps). (see diagram 1)

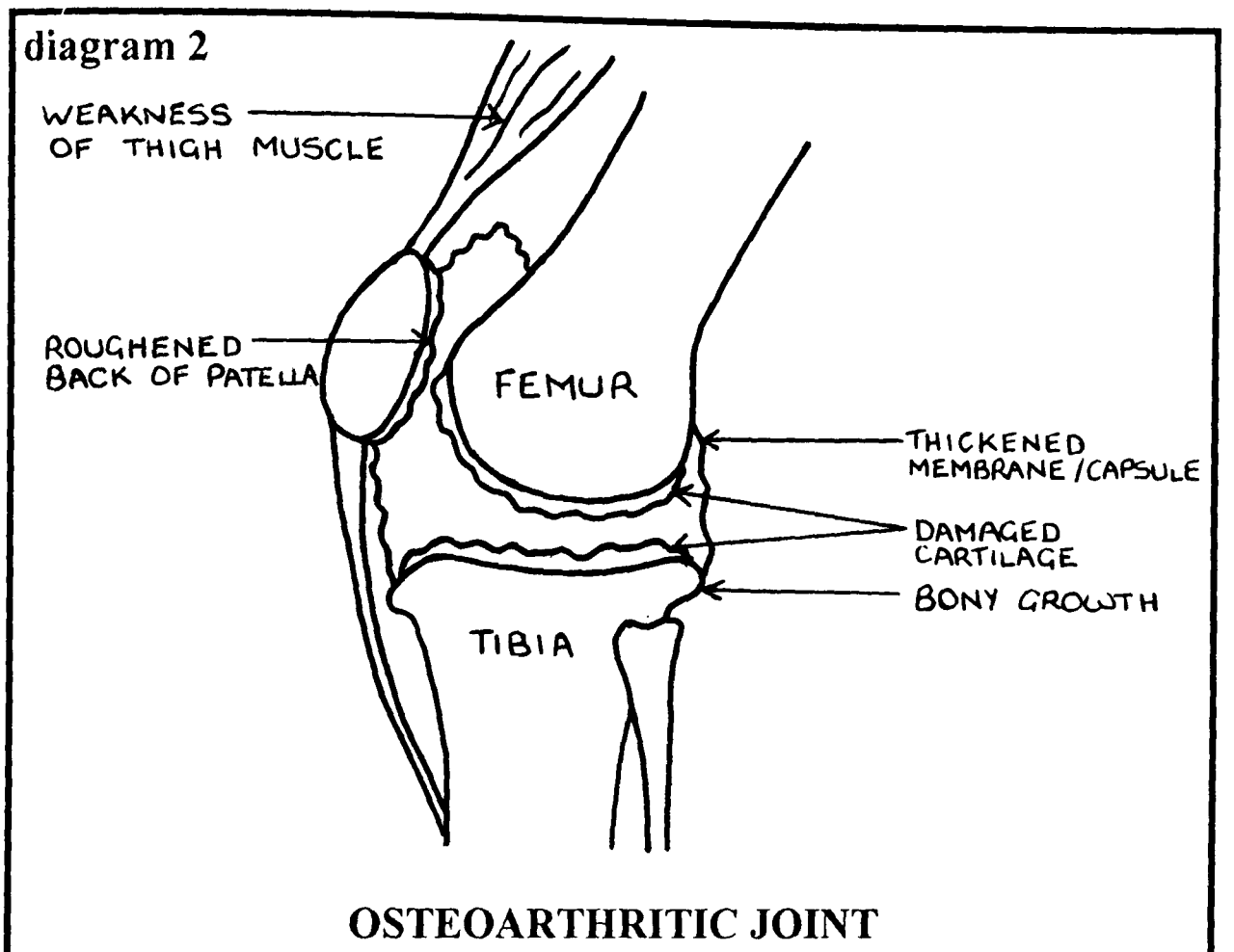
diagram 1



THE NORMAL KNEE JOINT

When someone has knee OA their cartilage becomes thinner and it's surface roughened. The bone underneath becomes thicker and grows out at the side of the joint as if it was trying to reduce the amount of possible movement. The synovial membrane usually becomes a little inflammed and extra fluid forms, making the

joint swell slightly. The capsule and ligaments may thicken and get stretched. In severe cases there may be quite a lot of damage to the cartilage, exposing the bone underneath. Deposits of crystals may form in the remaining cartilage and synovial membrane and float around in the fluid. (see diagram 2)



OSTEOARTHRITIC JOINT

Although osteoarthritis often causes no trouble, in some cases damage caused to the joint may result in pain and difficulty with movement. Osteoarthritis tends to develop very slowly over a period of months or years. Symptoms are usually variable, you may get good and bad days. In a very few cases constant pain develops even during rest at night.

There is no actual known cure for osteoarthritis and treatment is thus aimed at relieving or reducing the symptoms of pain and stiffness.

SELF HELP IN CONTROLLING KNEE PAIN

1. **Keeping your weight at a sensible level:** If you are overweight, losing weight will reduce the stress on your joints, particularly your knees which have to support your whole body.

2. **Exercise:** Resting for long periods may cause the joints to stiffen badly, while too much exercise may cause a great deal of pain. The general advice is to do a little exercise often and strike a balance between too much activity and too much rest. Exercise can help maintain the full range of movement in the knee. It also helps to keep the muscles surrounding your knee strong to protect and stabilise the joint. Swimming and walking (in sensible shoes!) are particularly good exercises for the knees.

3. **Foot wear:** Shoes with shock absorbing air cushioned soles help reduce jolting of the knee joint when walking. Footwear such as trainers are kind to the knees.

4. **Pain-killing Tablets:** Paracetamol can often help, it may be helpful to take this regularly at full dose, but never exceed the doses advised on the label. If these do not work for you go and see your doctor who may be able to prescribe you some alternative pain-killing tablets, unfortunately though their effectiveness is not absolutely guaranteed, they may work in some people but not others.

5. **Herbal Remedies:** There are a number of remedies on sale in health food shops which claim to be beneficial for arthritis. There is little evidence to suggest wether they do help or not, however there is no harm in trying them if you feel they may work for you.

6. **Copper Bracelets:** Again despite popular belief copper bracelets have no beneficial effects on osteoarthritis, although some peoples faith in them seems to help them.

7. **Local Heat Applications:** Although it does not have a long term effect local warmth often relieves pain and stiffness in osteoarthritic joints. Heat lamps are available commercially but a similar effect can be achieved more cheaply with hot water bottles wrapped in a towel (be careful, it is easy to burn yourself with either). Local heat should **not** however be used in cases where the joint is red or inflammed, or applied for longer than 20 to 30 minutes at a time.

8. **Local Cold Applications:** Some people may find local cold applications helpful (as an alternative to local heat) in relieving painful or swollen joints. Make an ice pack by wrapping a packet of frozen peas in a damp towel. The cold application should be applied at a comfortable level of coldness and for no longer than 10 to 15 minutes at a time.

9. **Relaxation:** If you do happen to be in pain try to concentrate on something that will take your mind from it. For example listen to some music or the television, or perhaps read a book.

Appendix 5: Satisfaction questionnaire

ABOUT THE STUDY

The following questions concern your experience with our study. Please answer all of the following questions as fully as possible.

1. Could you summarise your main reasons for agreeing to take part in this study?

2. Have you benefited from your participation in this study?

☐ Yes

☐ No

Please explain:

3. Have you incurred any injuries or adverse reactions as a result of your participation in this study?

☐ Yes

☐ No

If yes, please explain:

4. Have you incurred any costs as a result of your participation in this study?

☐ Yes

☐ No

If yes, please explain:

5. In the last 12 months have you been to a private hospital for any of the following, as a result of you **knee pain**? (Do NOT include G.P referrals)

Treatment Type	**Number of Sessions / Tests**
Consultations:	
X-rays:	
Blood Tests:	
Other tests: (Please specify)	
Arthroscopy:	
Knee Replacement:	
Other Treatment: (Please specify)	

6 In the last 12 months have you attended any of the following as a result of your **knee pain?**

Treatment Type	**Number of Sessions**
Private Physiotherapy:	
Osteopath / Chiropractor:	
Homeopathy / Aromatherapy:	
Toning Tables:	
Other (please specify):	

7. In the last 12 months have social services provided any of the following as a result of your **knee pain**?

	Yes	No
• Home aids (e.g. installation of shower, rails or ramps)	☐	☐
Please specify: _____		
• Meals on wheels	☐	☐
• Home help	☐	☐
• Other (please specify): _____		

Did you make a contribution towards the cost of any of the above?

☐ Yes ☐ No

If yes, which ones? _____

How much did you contribute? _____

8. Do you, or any member of your household, claim any of the following as a result of **your knee pain**?

	Yes	**No**
Disability living allowance	☐	☐
Mobility allowance	☐	☐
Attendance allowance	☐	☐
Carers allowance	☐	☐
Incapacity benefit	☐	☐

Other (please specify) _____

9. Since the start of this study, has your level of physical activity changed? (This DOES NOT include any exercises you may have been given as part of this study).

☐ Yes, I am more active now than I was at the start of the study.

☐ I am neither more nor less active than I was at the start of the study.

☐ No, I am less active than I was at the start of the study.

Was this change influenced in any way by your participation in the study?

☐ Yes ☐ Unsure

☐ No

10. Since the start of this study have you lost weight?

☐ Yes ☐ Unsure

☐ No

If yes, was this change influenced in any way by your participation in this study?

☐ Yes ☐ Unsure

☐ No

11. Have you use any of the following products during the period of the study?

☐ creams / gels (not supplied by your doctor).

☐ calcium supplements.

☐ vitamin supplements.

☐ cod liver oil.

☐ copper bracelets.

☐ other (Please specify _____)

Instructions:

*We are interested both in how much help you feel you **need**, and how much help you **get**, in performing your usual daily activities. For each of the following activities, could you say whether or not you need any help, and whether you do in fact receive assistance either from family or friends?*

Firstly, it would help us to know if you live alone, with family or in warden aided accommodation?

☐ alone ☐ partner ☐ family ☐ warden aided

Example: You need help to do your shopping and you receive that help from your neighbour. Your knee problems play a large part in causing this difficulty.

Your response would be as seen below.

Activity	Need Help?	Get Help?	Source of help?	Paid?	Knee related?
	Yes / No	Yes / No	Live-in = 1 Live-out = 2	Yes /No	Yes / No
Example (See above)	Yes	Yes	2	No	Yes
Shopping					
Cooking					
Light domestic duties					
Heavy domestic duties					
Having a bath					
Having a shower					
Dressing e.g. putting on socks and stockings.					
Rising from bed					
Walking					
Getting in/out of a car					

Appendix 6: Exercise diary

KNEE PAIN
INTERVENTION STUDY

EXERCISE DIARY

NAME:.....

STARTING DATE:.....

FINISHING DATE:.....

Funded by the Department of Health

ABOUT THE EXERCISES

Exercise is very important for everyone. For someone with knee pain however, it is particularly important. When joints are painful and therefore not used as much, the muscles around them tend to get weaker and this may cause further pain and damage. These exercises are designed to strengthen the muscles around the knee, particularly the thigh (quadriceps) muscles. We think you will find the exercises fun to do and should only take you about 20 minutes each day. You will find a diary at the back of this booklet in which to record your efforts.

General Advice:

- Exercise in a warm room in clothes which are not too tight.
- Build the exercises into your daily routine and do them at a time of day when you are least likely to be disturbed. If you like you can split up the exercises and do a few at various times throughout the day.
- Whilst exercising, rest your hands on your thighs so that you can feel the muscles working.
- If you do not manage to exercise on a particular day **do not** do double the next day.
- Increasing muscle strength is a slow process so do not become discouraged if you can not see an improvement immediately. Do not stop exercising.

- It is better to do a few strong exercises than lots of weak ones. There is no need to get breathless, take your time and rest in between each exercise.

- **Do not** do more than the maximum recommended amount for each exercise. As you feel comfortable with the exercises build them up.

Pain:

- As with any new exercise, there may be some fatigue or muscle ache. This is only a sign that the muscle has been working and is nothing to worry about. If the exercises are proving too difficult, cut down slightly and try to gradually build them up again.

- Try to do the exercises when you knees are not too painful. Take painkillers if necessary and do the exercise once they have started to work.

- If you experience a lot of pain whilst doing the exercises, stop for the day and cut back on the number of exercises you were doing.

If you have any questions or concerns, please phone your therapist ..... for advice.
Tel: (0115) 9691169 ext.45557

THE EXERCISES

The exercises are arranged in five sections:

Section A ⇒ Flexibility Exercises
Section B ⇒ Unresisted Exercises
Section C ⇒ Resisted Exercises
Section D ⇒ Functional Exercises
Section E ⇒ Aerobic Exercises

There are several exercises in each section. It is expected that you will work through the sections one at a time, doing at least two of the exercises each day. Please remember though that the more you do the more likely you are to feel some benefit from these exercises. When you find each exercise becoming easy, move on to one you find harder to do.

<u>Do not</u> progress through the exercises in section D and E until you have been told to do so by your therapist.

Exercise equipment:

As you progress to Section C of the exercise program your therapist will give you a large elastic band to make your muscles work harder. These come in various thicknesses, so you can progress from easy thin ones to tougher thick ones (doubling the thin ones makes the exercises harder).

- Keep it as wide as possible so that it doesn't dig into the leg when exercising. You could try some padding around your leg for comfort (e.g. socks padded with cotton wool or cloth).

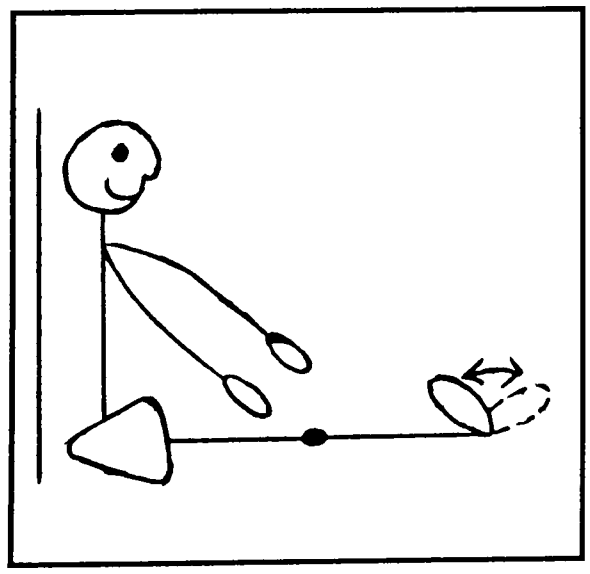
Untie all knots after exercising - this will help it to last longer. Storing the band in a plastic bag with a little talcum powder will make untying the band easier.

SECTION A: FLEXIBILITY EXERCISES

These exercises are designed to increase the range of movement in the knee and ankle before you begin the strengthening program.

Repeat the exercises in section A **five times**. Gradually build up to a maximum of **twenty** for each leg.

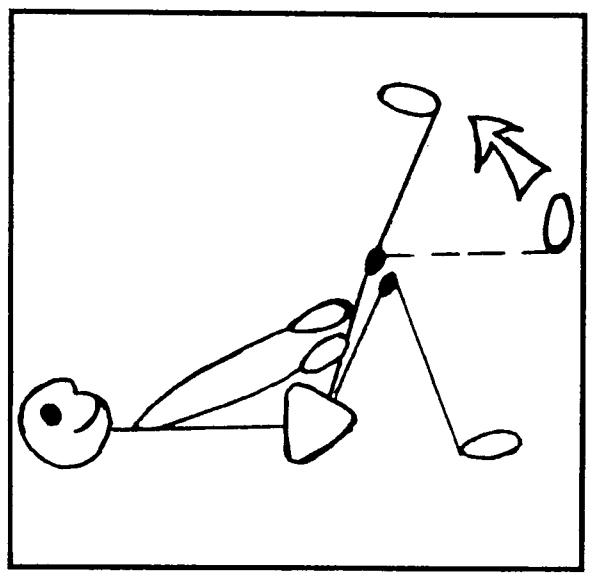
A1 Sitting on the floor (or bed)



Sit with your back supported and both your legs straight out in front and your toes pointing to the ceiling. Each ankle is then extended and flexed by pointing the toes and then flattening the foot.

BASIC

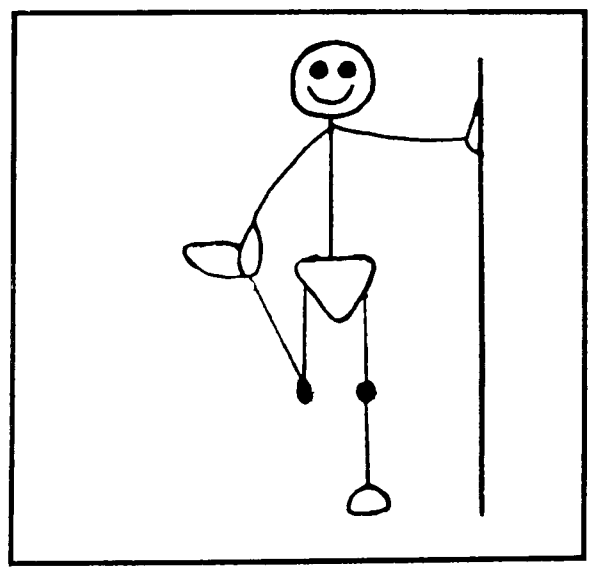
A2 Lying on the bed (or floor)



Lie on your back and bend your knees. Then in turn straighten each leg as far as possible and hold in this position for five seconds

BASIC

A3 Standing up (or lying on your side or front on the floor or bed)



Use a wall for balance and stand on one leg. Bend the other knee and bring your foot towards your bottom. Support your foot in your hand. If you find this difficult to do the exercise lying on your side or front.

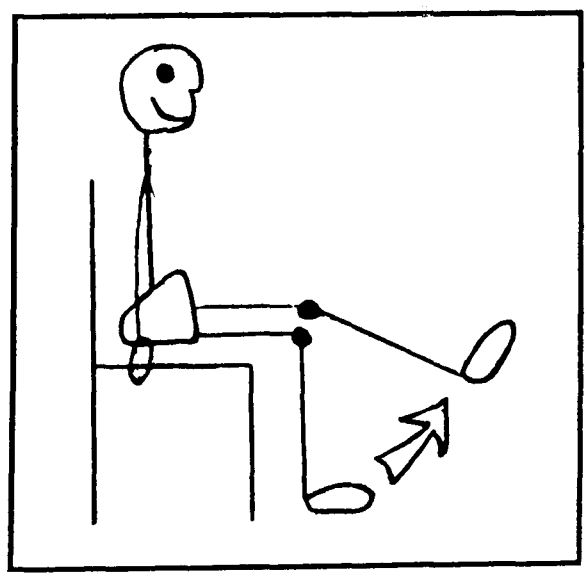
DIFFICULT

SECTION B: UNRESISTED EXERCISE

These are gentle strengthening exercises to start building up the muscles around the knee.

Hold the positions for **five seconds**. Repeat each exercise **five times** for each leg. Gradually build up to **twenty**.

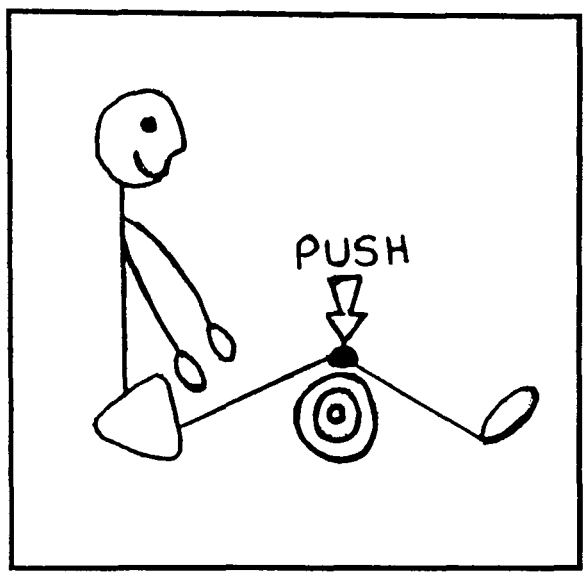
B1 Sitting in a chair



Sit upright in a high chair e.g. dining chair. Support your back by holding on to the seat with your hands. Now straighten one leg out in front of you.

BASIC

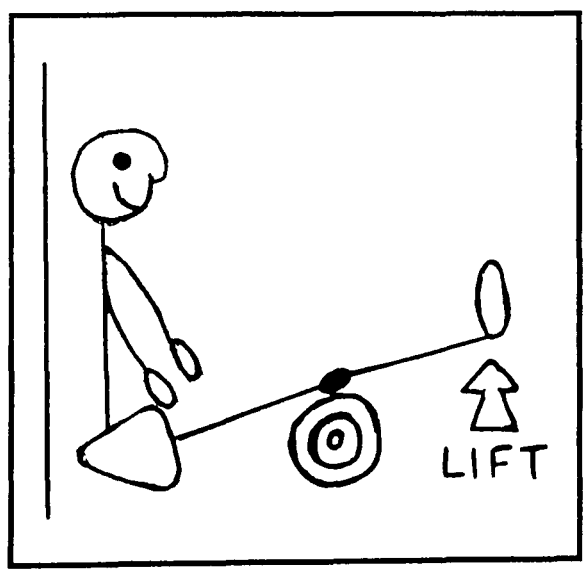
B2 Sitting on the floor (<u>no</u> back support)



Start with both your legs out in front of you, toes pointed towards the ceiling, with a rolled up towel beneath one knee to make it slightly bent. Try to push that knee back into the floor so that the thigh muscle tightens. Hold this position for five seconds.

BASIC

B3 Sitting on the floor (back supported)



Start with both legs out in front of you, toes pointing to the ceiling and back supported by a wall. Place a firm support beneath your knees. This should be very firm and almost too big to get your hands around (e.g. a thick towel rolled around a milk bottle). Straighten this leg with the back of the knee still in contact with the roll; the foot should leave the floor.

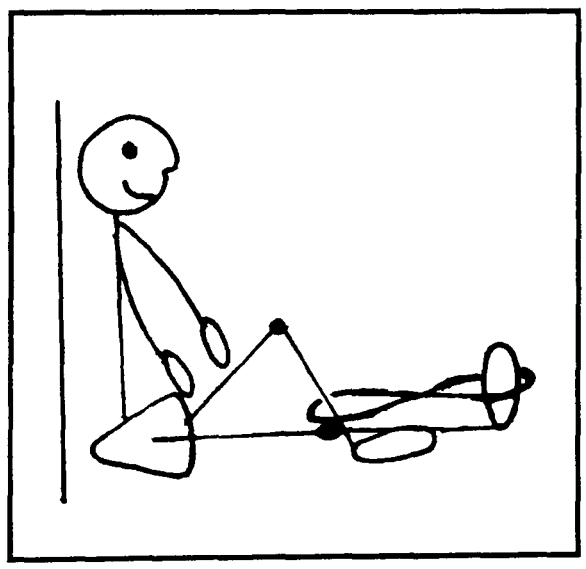
MORE DIFFICULT

SECTION C: RESISTED EXERCISE

These exercises are designed to give the thigh muscles more work to do by having them stretch out large elastic bands.

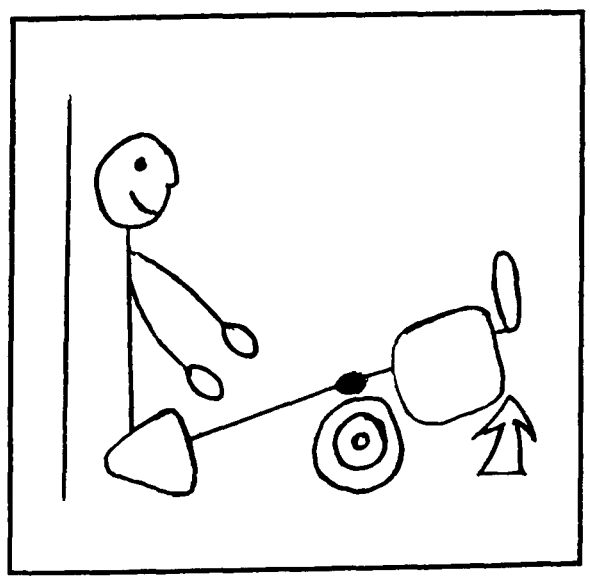
Hold the positions for **five seconds**. Repeat each exercise **five times** for each leg. Gradually build up to **twenty**.

C1 Sitting on the floor (back supported)



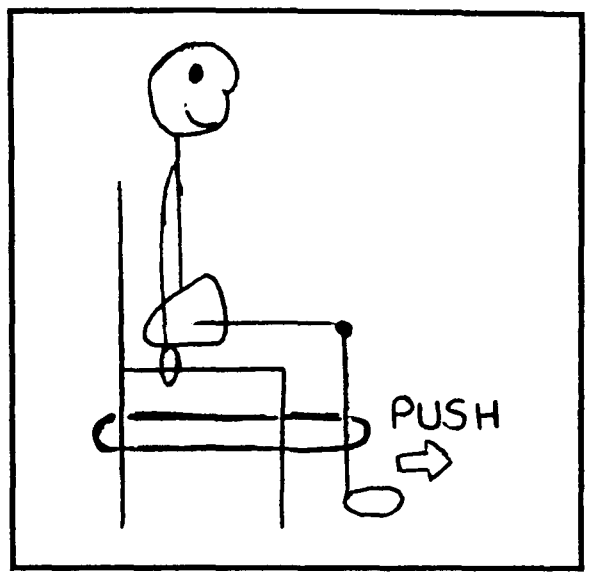
Sit on the floor with your back supported by a wall. Bend both your knees. Tie the exercise band loosely around one ankle. Twist it into a figure of eight and put the new loop over the instep of the other foot. Now try and straighten the latter leg

C2 Sitting on the floor (back supported)



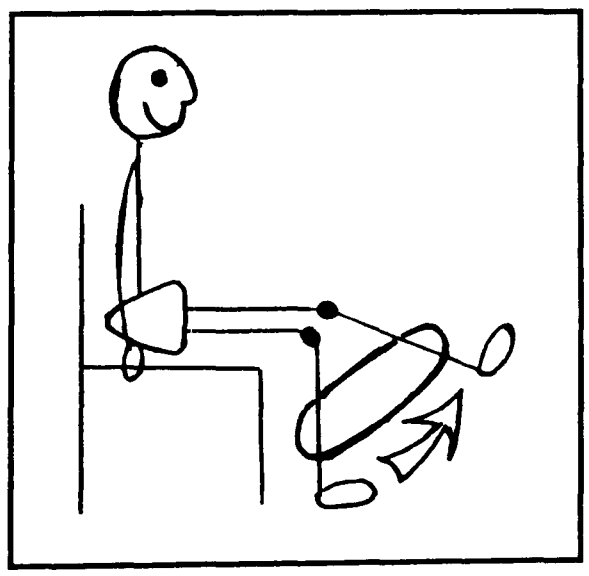
Sit on the floor with your knee supported as for exercise B3. Place a pillow over the ankle of one leg. Straighten this leg with the back of the knee still in contact with the roll. This is harder than B3 because of the pillow.

C3 Sitting in a chair



Sit upright in a high chair, your knees should be bent at right angles. Tie a strong elastic band around the ankle of one leg and the back chair leg. The band should be tied tight enough so that there is no slack, but not so tight that it is uncomfortable. Now try to push against the band with your leg as hard as you can as though you are trying to straighten it. Support your back by holding on to the seat with your hands. Use padding around your ankle.

C4 Sitting in a chair



Sit upright in a high chair. With your feet together tie the elastic band around your ankles (the band should be tight enough so that there is no slack in it, but not so tight that it is uncomfortable, use padding around your ankle if necessary). Straighten one leg out as far as you can, keeping the other leg still. Support your back by holding on to the seat with your hands.

SECTION D: FUNCTIONAL EXERCISES

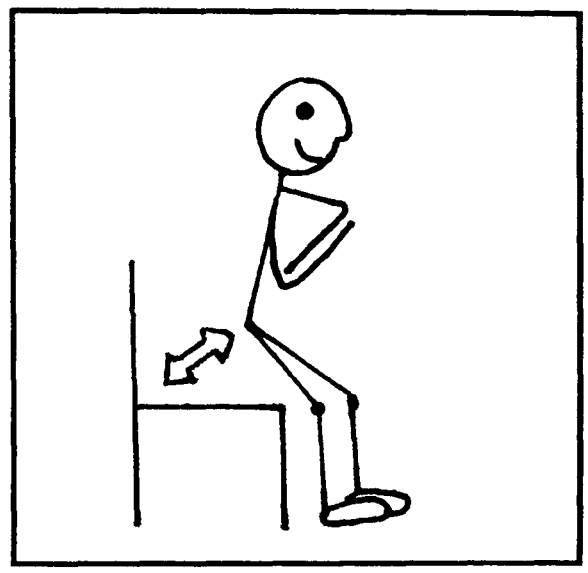
These are exercises designed to help directly with the tasks of every day life. They should become easier as your strength develops.

PLEASE <u>DO NOT</u> DO THE EXERCISES IN SECTION D AND E UNTIL YOU HAVE BEEN TOLD TO DO SO BY YOUR THERAPIST.

Take your time when doing these exercises, there is no need to get breathless. Take a rest in between each exercise if necessary.

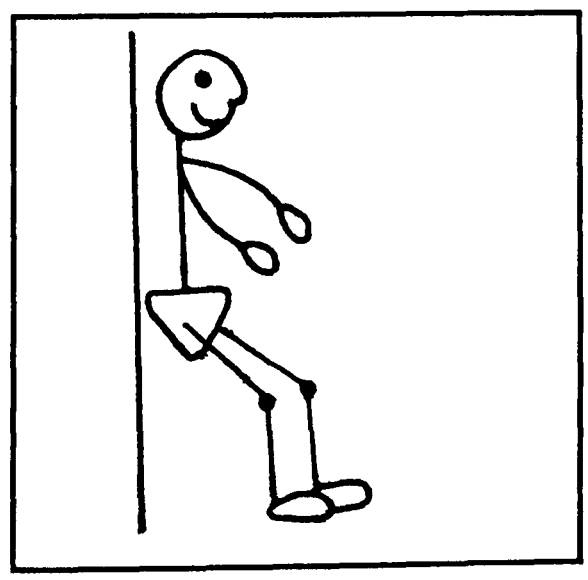
The exercises in Section D should be repeated **<u>five times</u>** for each leg. Gradually build up to **<u>twenty</u>**.

D1 Rising from sitting



Sit in a chair with your arms folded across your chest. Now try to get up from the chair without using your arms to push yourself up. Try to do this exercise in a high chair to start with but as it becomes easier to do try to sit in a lower chair.

D2 Standing



Stand with your back leaning against a wall and feet slightly apart (approximately 12 inches from the wall). Slide your back down the wall, (only slightly to start with), so that you are in a squatting position and hold for five seconds. As you find this exercise easier to do try to get a little further down.

SECTION E: AEROBIC EXERCISES

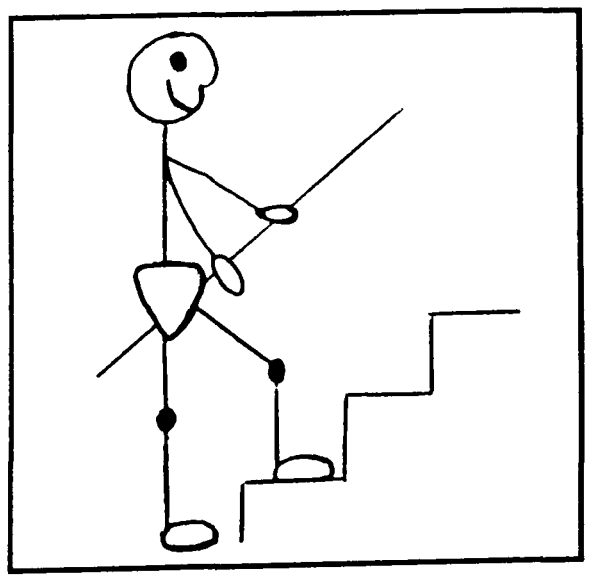
These exercises are also designed to help directly with the tasks of every day life. They should become easier as your strength develops.

PLEASE <u>DO NOT</u> DO THE EXERCISES IN SECTION D AND E UNTIL YOU HAVE BEEN TOLD TO DO SO BY YOUR THERAPIST.

Take your time when doing these exercises, there is no need to get breathless. Take a rest in between each exercise if necessary.

These exercises should be repeated **<u>five times</u>** for each leg. Gradually build up to **<u>twenty</u>**.

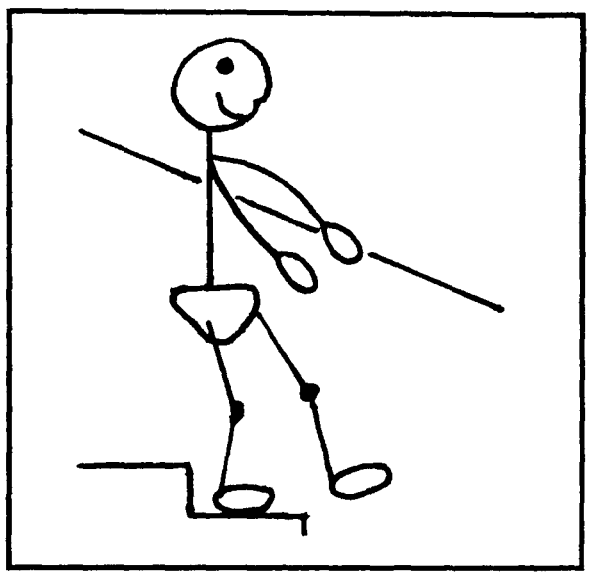
E1 Up and down a step



Use the lowest step of your stairs, step up onto the step with your right foot and follow with your left. Then step back down. Do this five times and repeat, this time leading with your left leg. Take a rest in between if necessary. Gradually build up to twenty times for each leg. You can use the banister for balance, but do not use it to pull yourself up.

EASY

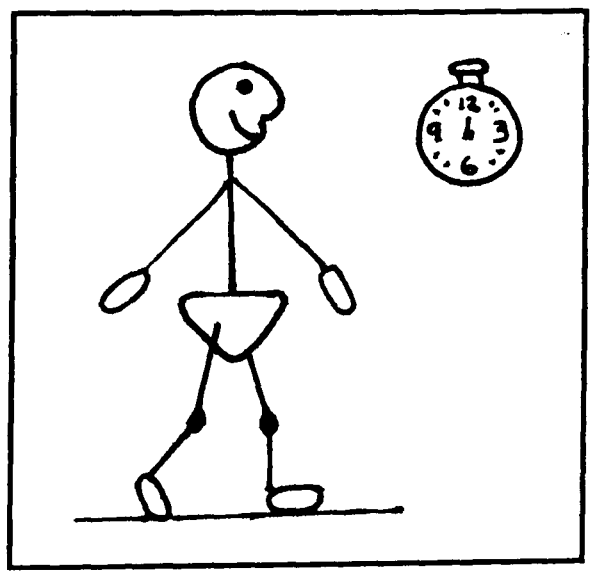
E2 Stepping down



Stand on the lowest step facing as though you are going down. With one leg step down but just before your foot hits the floor (about an inch from the ground). Hold this position for five seconds.

DIFFICULT - start carefully

E3 Walking



Plan yourself a walk around where you live. The walk should be about a mile in length. Take a walk using this route three times each week. Time yourself each time, and record the minutes in the back of this diary. Try to walk a little faster as the weeks go by.

NOTES:

Please use the space below to record any comments or difficulties you have had with the exercise programme.

EXERCISE DIARY

The following pages consist of your exercise diary. Please try to fill it in as accurately as possible. It is very important to us to get a picture of how much exercise you have done - so please fill out the diary honestly even if you have not been able to do any of the exercises.

- Please complete the exercise diary every day when you have finished exercising.
- Write down which exercises you have done and how many of each.
- If you do any additional exercise (e.g. walking, swimming etc.) please make a note of it in space marked "additional exercise" for the relevant day.
- If you miss a session or stop for any reason, please make a note of the reason in your diary and recommence as soon as possible. Do not worry about it, just start off gently again.
- Remember even if you go on holiday you can still continue with your exercise program.
- Your completed diaries will be collected by your therapist once they are full. If you run out of diary space, please continue to exercise and use the back page to record your exercises until your therapist visits you again.

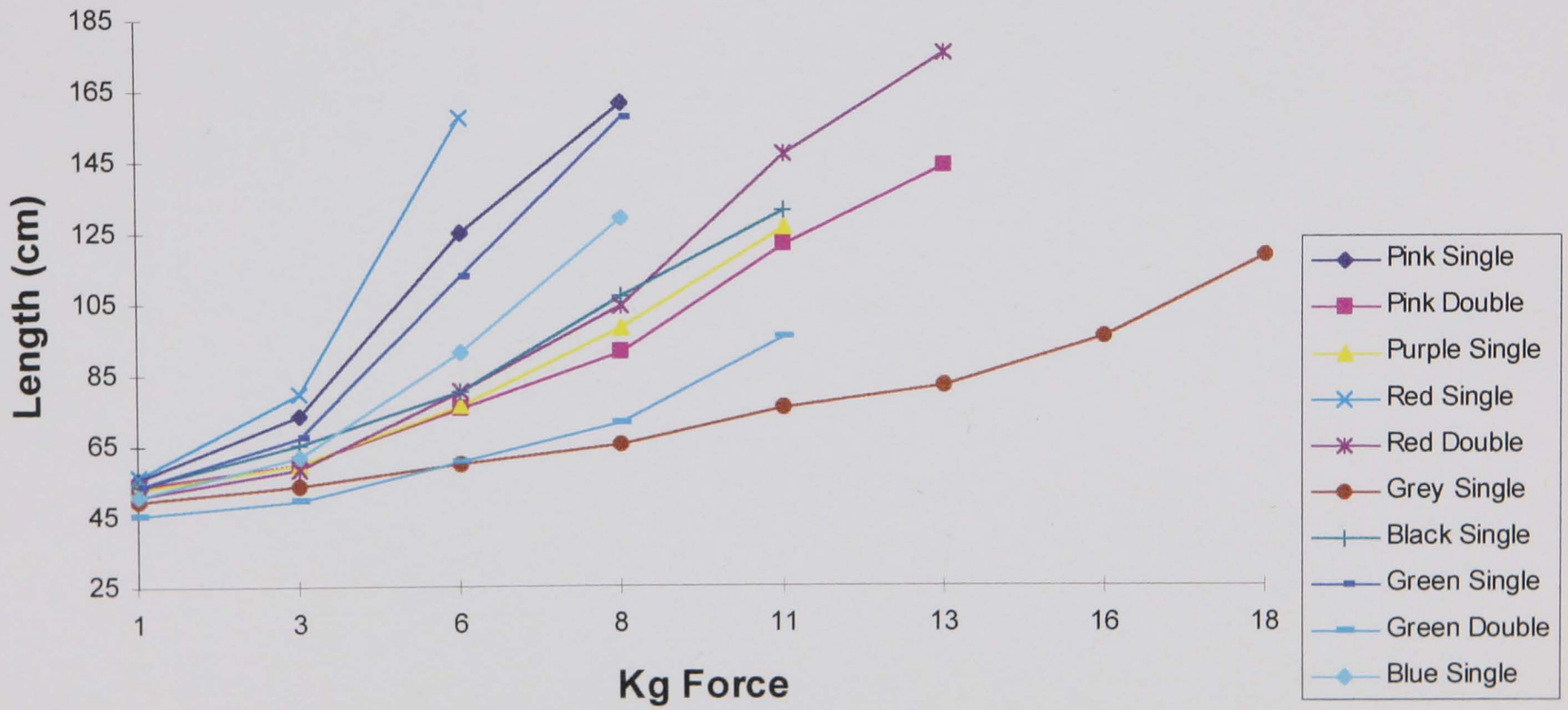
ENJOY THE EXERCISE PROGRAM

	MONDAY	TUESDAY	WEDNESDAY	TH
Date:				
Additional Exercise				
Date:				
Additional Exercise				
Date:				
Additional Exercise				
Date:				
Additional Exercise				
Date:				
Additional Exercise				

THURSDAY	FRIDAY	SATURDAY	SUNDAY

Appendix 7: Strength of exercise bands under laboratory conditions

Graph showing band strengths under laboratory conditions.



Appendix 8: Assessment of adherence

RATING OF TREATMENT ADHERENCE - DIARIES

1. Number of Days Exercising:

6	5	4	3	2	1
☐	☐	☐	☐	☐	☐
Nearly every day for 6 months.	Miss 1-2 days per week over 6 months.	Miss 2-3 days per week over 6 months.	Started keen - tailed off.	Missed 2-3 times in 1st 8 and few after.	Little or nothing.

2. Number of exercises done.

1	2
☐	☐
0 - 2	3 - 5

3. Number of repetitions.

1	2	3
☐	☐	☐
< 10	10	>10

Choose one from sections 1 - 3. Add together the scores and deduct 2 points. This will allow a score of 1 - 9 (9 being the best degree of compliance and 1 the worst).

Appendix 9: Telephone support checklist

TELEPHONE INTERVENTION MONITORING FORM

NAME. . . . . .

Ref No ☐☐☐☐☐☐

Start.....

1st Topic Introduced ☐

Time

Finish.....

Date:.....

Mins. ☐☐

Initials:.....

---

1. State of the Knees ☐
2. Medication/Alternative Therapies/Problems ☐
3. GP Visits ☐
4. Sleep patterns ☐
5. Social/Getting out and about ☐
6. Mood - How are you feeling ☐
7. Level of support required (in daily functions) ☐
8. General Health ☐
9. Any other pain ☐
10. Initiated topic from respondent ☐

If found, please return to Anna Follows ext: 45557.

Appendix 10: Case note abstraction forms

- GP abstraction form
- GP prescribed medicines abstraction form
- Hospital abstraction form
- Summary forms for GP, GP prescribed medicines and hospital costs

Case Note Abstraction – G.P. Notes

ame: _____ **Assessed:** __ / __ / __

ef: _____ **D of B:** __ / __ / __

PERIOD _____

From: _____ **To:** _____

.B. Don't record nurse visits (contact time or drugs given). If blood taken for tests – record as investigation, but nder one of the doctor's visits.

						Total:
Date(s):						
Knee Pain: 1 = yes 2 = % yes 3 = GI 4 = no 5 = unsure						1 = 2 = 3 = 4 = 5 =
Seen By: 1 = G.P. 3 = Phone						1 = 3 =
What was provided?	Investigation Number..... Drugs Number ..... Treatment Number ..... X-ray Number:..... Home visit YES/NO Night visit YES/NO	Investigation Number..... Drugs Number ..... Treatment Number ..... X-ray Number:..... Home visit YES/NO Night visit YES/NO	Investigation Number..... Drugs Number ..... Treatment Number ..... X-ray Number:..... Home visit YES/NO Night visit YES/NO	Investigation Number..... Drugs Number ..... Treatment Number ..... X-ray Number:..... Home visit YES/NO Night visit YES/NO	Investigation Number..... Drugs Number ..... Treatment Number ..... X-ray Number:..... Home visit YES/NO Night visit YES/NO	Investigations Number..... Drugs Number ..... Treat's Number ..... X-Ray Number:..... Home v's Number ..... Night v's Number .....
Comments						

Osteoarthritis? ☐ **Rheumatoid Arthritis?** ☐

Hospital treatments? **YES / NO**

Continued YES / NO (Please circle)

G.P Prescribed Medicines

Name: _____ Assessed: __ / __ / __

Ref: _____ D of B: __ / __ / __

PERIOD _____

From: _____ To: _____

* = repeat prescription

Drug Type	Dose	Amount	Number of presc's issued	BNF Code	Knee pain (from notes) 1=yes,2=% yes 3=no,4=unsure	Price per presc'n	Total Price

TOTAL DRUGS COST: £_____ **KNEE PRESCRIPTIONS:** _____

TOTAL PRESCRIPTION: _____ **RELATED PRESCRIPTIONS:** _____

Continued YES / NO (Please circle)

Case Note Abstraction – Hospital Notes

Name: _____ Ref: _____ D of B:__ / __ / __

PERIOD _____

From: _____ To: _____

Date:					Total:
Provider: 1=City, 2=QMC 3a=Private Hospital (paid by practice) 3b= Private Hospital (paid by self) 4=NHS out of region					1 = 2 = 3a= 3b= 4 =
Speciality:					
Reason: 1 = knee pain 2 = arthritis general (locomotor) 3 = G.I. 4 = not related					1= 2= 3= 4=
Service Type: 1=inpatient 2=daycase 3a=outpatient(new) 3b=outpatient(FU) 4 = A & E					1= 2= 3a= 3b= 4 =
Length of Stay: (Inpatients only)					
Days in ICU:					

If knee pain (1):

Seen By: Consultant (1) Registrar (2) SHO (3) Nurse (4) Other – specify (5)					1= 2= 3= 4= 5=
X-Ray: (Each knee = 1)					
Blood tests:					
Injections to joint:					
Drugs:					
Physio/Hydro /OT					
Other: (Specify)					
Operations: (Specify)					
Comments					

CONTINUED YES / NO

SUMMARY OF GP ABSTRACTION FORM

Period: _____ **1st Assessed: __ / __ / __**

Name: _____ Ref: ___ DoB: __ / __ / __

	KNEE	% KNEE	G.I	TOTAL
GP:				
Phone:				
Investigations				
Drugs				
Treatments				
X-rays				
Home visits				
Night visits				

Osteoarthritis (1): ☐ **Rheumatoid Arthritis (2):** ☐

DNA: _____ **Hospital: YES / NO**

Comments:

Entry complete: (Initial) ☐

PERIOD _____

Name:_____ **Ref:** _____

KNEE PAIN DRUGS (Those quoted by patient and G.P notes)

NSAIDs 10.1.1		RUBS/ GELS 10.3.2	ANALGESICS 4.7.1 or 4.7.2	GI DRUGS 1.3.1, 1.3.5 or 1.3.4		OTHER e.g. steroids 10.1.2 anti-depressants 4.3.1 < 50mg Quinine (if quoted by patient)
Normal	SR			<£5.50	>£5.50	
£	£	£	£	£	£	£

RELATED DRUGS (Any of above drugs not previously mentioned by patient)

NSAIDs 10.1.1		RUBS/ GELS 10.3.2	ANALGESICS 4.7.1 or 4.7.2	GI DRUGS 1.3.1, 1.3.5 or 1.3.4		OTHER e.g. steroids 10.1.2 anti-depressants 4.3.1 < 50mg Quinine (if quoted by patient)
Normal	SR			<£5.50	>£5.50	
£	£	£	£	£	£	£

Over the Counter Drugs

NSAIDS = _____ **ANALGESICS =** _____

RUBS/GELS = _____ **HEALTH FOODS =** _____

OTHER = _____

TOTAL DRUGS COST £_____ **KNEE PRESCRIPTIONS:** _____

TOTAL PRESCRIPTIONS: _____ **RELATED PRESCRIPTIONS:** _____

KR/drugs_summary_form/24/11/97

SUMMARY OF HOSPITAL ABSTRACTION FORM

Period: _____

Name: _____ **Ref:** _____

	Knee	% Knee	GI	Total
Inpatient:				
Length of stay				
Days in ICU				
Day case:				
Outpatient - new				
Outpatient – FU				
A & E				

Dep't 1 _____ **Dep't 2** _____ **Dep't 3** _____

Knee only (Code 1)

Consultant	
Registrar	
SHO	
Nurse Practitioner	
Other	
X-Ray	
Blood Tests	
Injections	
Drugs	
Physio/OT	
Other (Specify)	

	Knee	Total
City		
QMC		
Private (practice)		
Private (self)		
NHS Other		

Operation 1:

_____

Operation 2:

_____

Comments:

Appendix 11: Publications arising from this thesis

- Oral presentation: Society for Social Medicine, September 1999

Thomas, K and Miller, P. on behalf of the Osteoarthritis Research Group (1999) The cost-effectiveness of a home-based exercise programme in relieving the pain and disability of knee osteoarthritis. *Journal of Epidemiology and Community Health* **53**, S12.

Objective: To assess the cost-effectiveness of a home-based exercise programme in relieving the pain and disability of knee osteoarthritis.

Design: A two-year, single-blind, randomised factorial trial. Treatment arms included: exercise therapy, telephone social support, a placebo health food product and no intervention. Economic data were collected prospectively alongside the trial. Analysis was conducted on an intent-to-treat basis.

Setting: Community-based trial using two GP Practices in the Nottingham area.

Subjects: 500 women, 286 men aged 45 years and over. Initial recruitment via postal survey (n = 9,296).

Primary outcome: Self-reported knee pain at 24 months (assessed using WOMAC).

Results: Exercise therapy resulted in a significant reduction in knee pain, knee stiffness and knee related physical disability at 24 months (p=<0.001, 0.01 and <0.001 respectively). Effect sizes were modest, but improvements were incremental to normal care. The number needed to treat (NNT) in order to achieve a ≥ 50% reduction in pain at 24 months for a single individual was between 8 and 13. The cost per person of the two-year exercise programme was £112.48. Analysis of GP records revealed no change in the use of either arthritis related services or total medical costs during the first 12 months of the trial. The cost of achieving a clinically significant outcome in a single individual (based on NNT figures) was £1,012.

Conclusion: Home-based exercise therapy could be a very cost-effective treatment option for the management of knee pain in the community. Further research is required in order to assess its impact on medical costs in the longer term.