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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 01/09/02. The contractual start date was in July 2002. The draft report began editorial review in December 2006 and was accepted for publication in July 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study

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Objectives: To determine whether GPs should advise their older patients with chronic knee pain to use topical or oral non-steroidal anti-inflammatory drugs (NSAIDs).

Design: An equivalence study was designed to compare the effect of advice to use preferentially oral or topical ibuprofen (an NSAID) on knee pain and disability, NSAID-related adverse effects and NHS/societal costs, using a randomised controlled trial (RCT) and a patient preference study (PPS). Reasons for patient preferences for topical or oral preparations, and attitudes to adverse effects, were explored in a qualitative study.

Setting: Twenty-six general practices in the UK.

Participants: Participants comprised 585 people with knee pain, aged 50 years or over; 44% were male, mean age 64 years. The RCT had 282 participants: 144 in the oral group and 138 in the topical group. The PPS had 303 participants: 79 in the oral group and 224 in the topical group.

Interventions: Advice to use preferentially oral or topical NSAIDs for knee pain.

Outcome measures: The primary outcome measure was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary outcome measures were the Short Form with 36 Items (SF-36), perceived troublesomeness of knee pain, satisfaction with health status, major adverse effects (unplanned hospital admissions and deaths) and minor adverse events over 12 months. The health economic analysis measured the comparative cost per quality-adjusted life-year (QALY) from both an NHS and a societal perspective over 1 and 2 years.

Results: Changes in the global WOMAC score at 12-months were equivalent in both studies: topical – oral, RCT difference = 2 [95% confidence interval (CI) –2 to 6], PPS difference = 1 (95% CI –4 to 6). There were no differences in the secondary outcomes, except for a suggestion, in the RCT, that those in the topical group were more likely to have more severe overall pain and disability as measured by the chronic pain grade, and more likely to report changing treatment because of inadequate pain relief. There were no differences in the rate of major adverse effects but some differences in the number of minor ones. In the RCT, 17% and 10% in the oral and the topical group, respectively, had a defined respiratory adverse effect (95% CI of difference –17% to –2.0%); after 12 months, the change in serum creatinine was 3.7 mmol/l (95% CI 0.9 to 6.5) less favourable in the oral than in the topical group, and 11% of those in the oral group reported changing treatment because of adverse effects compared with 1% in the topical group ($p = 0.02$). None of these differences were seen in the PPS. Oral NSAIDs cost the NHS £191 and £72 more per participant over 1 year in the RCT and PPS respectively. In the RCT the cost per QALY in the oral group, from an NHS perspective, was in the range £9000–12,000. In the PPS it was £2564 over 1 year, but over 2 years the oral route was more cost-effective. Patient preference for medication type was affected by previous experience of medication (including adverse reactions), other illness, pain elsewhere, anecdotes, convenience, severity of pain and perceived degree of degeneration. Lack of understanding about knee pain

and the action of medication led to increased tolerance of symptoms. Potentially important symptoms may inadvertently have been disregarded, increasing participants' risk of suffering a major adverse effect. **Conclusions:** Advice to use either oral or topical preparations has an equivalent effect on knee pain, but oral NSAIDs appear to produce more minor adverse effects than topical NSAIDs. Generally, these results support advising older people with knee pain to use topical rather than oral NSAIDS. However, for patients who prefer oral NSAID preparations rather than a topical NSAID, particularly those with more widespread or severe pain, the oral route is a reasonable treatment option, provided that patients are aware of the risks of potentially serious adverse effects from oral medication. Further research is needed into strategies to change prescribing behaviour and ensure that older patients are aware of the potential risks and benefits of using NSAIDs. Observational studies are needed to estimate rates of different predefined minor adverse effects associated with the use of oral NSAIDs in older people as are long-term studies of topical NSAIDs in those for whom oral NSAIDs are not appropriate.

Contents

List of abbreviations

A&E	accident and emergency
ACR	American College of Rheumatologists
AUC	area under the curve
BP	blood pressure
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DDD	defined daily dose
EMIS	Egton Medical Information Systems
EQ-5D	EuroQol instrument
FEV_1	forced expiratory volume in 1 second
FNA	first nurse assessment
GPRF	General Practice Research Framework
Hb	haemoglobin
HRG	Health Resources Group
IAQ	initial approach questionnaire
ICER	incremental cost-effectiveness ratio
MA	medical assessment
MR	medical record
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
OR	odds ratio
PEF	peak expiratory flow rate
PPS	patient preference study
PSS	Personal and Social Services
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SD	standard deviation
SEA	study entry assessment
SF-36	Short Form with 36 Items
TOIB	Topical or Oral IBuprofen
VAS	visual analogue scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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

Executive summary

Background

Both oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat knee pain. However, oral NSAIDs are associated with gastric, renovascular and respiratory adverse effects, which are a particular risk for older people. If oral and topical NSAIDs are equally effective for chronic knee pain, and topical preparations produce fewer adverse effects than oral preparations, they may be preferred to oral preparations, even if they appear more expensive to purchase. Patient preference for route of administration may be an important factor influencing patient perception of effectiveness of the medication.

Objective

The objective of the study was to determine whether GPs should advise their older patients with chronic knee pain to use topical or oral NSAIDs.

Design

An equivalence study was designed to compare the effect of advice to use preferentially oral or topical ibuprofen (an NSAID) on knee pain and disability, NSAID-related adverse effects and NHS/societal costs, using a randomised controlled trial (RCT) and a patient preference study (PPS). Reasons for patient preferences for topical or oral preparations, and attitudes to adverse effects, were explored in a qualitative study.

Setting

The setting was 26 general practices in the UK.

Participants

Participants comprised 585 people with knee pain, aged 50 years or over; 44% were male, mean age 64 years. The RCT had 282 participants: 144 in the oral group and 138 in the topical group. The PPS had 303 participants: 79 in the oral group and 224 in the topical group.

Intervention

The intervention was advice to use preferentially oral or topical NSAIDs for knee pain.

Main outcome measures

The primary outcome measure was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary outcome measures were the Short Form with 36 Items (SF-36), perceived troublesomeness of knee pain, satisfaction with health status, major adverse effects (unplanned hospital admissions and deaths) and minor adverse events over 12 months. The health economic analysis measured the comparative cost per quality-adjusted life-year (QALY) from both an NHS and a societal perspective over 24 months.

Results

Clinical outcomes

Changes in the global WOMAC score at 12-months were equivalent in both studies: topical – oral, RCT difference = 2 [95% confidence interval (CI) –2 to 6], PPS difference = 1 (95% CI –4 to 6). There were no differences in the secondary outcomes, except for a suggestion, in the RCT, that those in the topical group were more likely to have more severe overall pain and disability as measured by the chronic pain grade, and more likely to report changing treatment because of inadequate pain relief.

Adverse effects

There were no differences in the rate of major adverse effects. There were some differences in the number of minor adverse effects. In the RCT, 17% and 10% in the oral and the topical group, respectively, had a defined respiratory adverse effect (95% CI of difference –17% to –2.0%); after 12 months, the change in serum creatinine was 3.7 mmol/l (95% CI 0.9 to 6.5) less favourable in the oral than in the topical group, and 11% of

those in the oral group reported changing treatment because of adverse effects compared with 1% in the topical group ($p = 0.02$). None of these differences were seen in the PPS.

Economic analysis

Oral NSAIDs cost the NHS £191 and £72 more per participant over 1 year in the RCT and PPS, respectively. In the RCT the cost per QALY in the oral group, from an NHS perspective, was in the range £9000–12,000. In the PPS it was £2564 over 1 year, but over 2 years the oral route was dominant, that is, more cost-effective.

Qualitative studies

Patient preference for medication type was affected by previous experience of medication (including adverse reactions), other illness, pain elsewhere, anecdotes, convenience, severity of pain and perceived degree of degeneration. Lack of understanding about knee pain and the action of medication led to increased tolerance of symptoms. Symptoms such as indigestion, sensitive stomach and poor general well-being were normalised as an effect of age rather than medication. Potentially important symptoms may inadvertently have been disregarded, increasing participants' risk of suffering a major adverse effect.

Interpretation

Clinical outcomes in the two groups were similar in almost every measure at every time-point. This finding was consistent across the RCT and PPS, suggesting that the two treatment strategies are either equally effective or equally ineffective. Although it is inconclusive, those in the RCT oral group appeared to have more minor adverse effects. Rigorous safety exclusion criteria meant that the impact of adverse effects on NHS costs and health utility may have been underestimated. Since the absolute differences in NHS costs and health utility were small, the cost per QALY may have been very sensitive to any such underestimate. In the PPS, participants with more severe widespread pain chose oral rather than topical ibuprofen. Furthermore, there was little difference in defined adverse effect rates in those who chose oral NSAIDs and those who were randomised to them, even though the PPS oral group took substantially more oral NSAIDs and were older than those in the RCT.

Conclusions

Advice to use either oral or topical preparations has an equivalent effect on knee pain, but oral NSAIDs appear to produce more minor adverse effects than topical NSAIDs. Generally, these results support advising older people with knee pain to use topical rather than oral NSAIDS. However, for patients who prefer oral NSAID preparations rather than a topical NSAID, particularly those with more widespread or severe pain, the oral route is a reasonable treatment option, provided that patients are aware of the risks of potentially serious adverse effects from oral medication.

Implications for healthcare

The evidence suggests that advice to use topical NSAIDs in preference to oral NSAIDs for treating knee pain in older people may be appropriate.

Recommendations for research

Further research is recommended in the following areas.

- Developing and testing strategies to change prescribing behaviour and ensure that older patients are aware of the potential risks and benefits of using NSAIDs.
- Observational studies to estimate rates of different predefined minor adverse effects associated with the use of oral NSAIDs in older people.
- Long-term studies of topical NSAIDs in those for whom oral NSAIDs are not appropriate, for example the very elderly.

Chapter 1
Introduction

Knee pain and knee osteoarthritis in older people

The focus of this report is the management of knee pain in older people. For the purposes of this study, older people are defined as those aged 50 years or over, around one-third of whom suffer from knee pain.[1–4] Half of these have severe difficulty with physical function or severe pain.[5,6] Despite the fact that there is an imprecise relationship between knee pain and the presence of radiological osteoarthritis (OA), much knee pain is attributed to OA. A systematic review of the literature about this relationship found that 36–50% of those aged 45 years or over with knee pain had radiological OA and that 24–56% of those with radiological OA had knee pain.[7] The variability in the relationship between knee pain and OA in the 13 studies reviewed is thought to be due to both the different wording of the questions used to elicit knee pain and the different views used in radiological assessments.[7]

The American College of Rheumatologists' (ACR) clinical definition of knee OA does not depend on radiological evidence (*Figure 1*).

This definition was developed for the purpose of separating cases of knee pain due to degenerative problems from those due to inflammatory arthritis in a North American secondary care population.[8] It is not clear how well such a definition transfers for use in a UK primary care population. Its original validation found it to be 95% sensitive and 69% specific. The weaknesses of these diagnostic criteria are well recognised.[9,10] Nevertheless, they are recommended and have some utility for our current purpose; most people aged 50 years or over who have chronic knee pain will satisfy these diagnostic criteria.[11] However, in a community study only 44% of those satisfying these criteria had symptomatic radiographic knee OA.[10]

- Knee pain
- Plus three of
  - Age >50 years
  - Stiffness <30 minutes
  - Crepitus
  - Bony tenderness
  - Bony enlargement
  - No palpable warmth

FIGURE 1 *ACR Diagnostic criteria for clinical diagnosis of knee OA*

We recognise that:

- Many older people with knee pain will not have radiological evidence of OA.
- Many people with radiological OA are not troubled by knee pain.
- Even if radiological OA is present, it may not be the cause of their pain.

However, the majority of older people with chronic knee pain will meet the ACR clinical criteria for OA. This reflects the pragmatic approach to managing chronic knee pain in older people commonly used in primary care.[12] In particular, patients present for treatment of their symptoms, not for treatment of a radiological observation. For the remainder of this report, we will describe our subjects as suffering from knee pain. When referring to others' work we will, unless specified otherwise, use the terms knee pain or OA as applied by the original authors irrespective of the definitions they used for these.

This report compares advice to use topical and oral non-steroidal anti-inflammatory drug (NSAID) medication for chronic knee pain (>3 months' duration) in people aged 50 years or over for which there does not appear to be an inflammatory cause.

Drug treatment of knee pain in older people

A wide range of conservative interventions are used to manage knee pain in older people.[13] Oral NSAIDs are one of the most commonly used conservative treatments for knee OA.[14] NSAIDs inhibit the action of the enzyme cyclooxygenase, thus reducing the production of prostaglandins that mediate inflammation and pain. In the short term, NSAIDs do reduce pain in those with knee

OA.[15,16] One study of oral NSAIDs found an overall effect size of 10.1 mm on a visual analogue scale (VAS) over a period of 2–13 weeks; however, longer term the data are equivocal.[15,17–19] There are some data suggesting a long-term benefit from one COX-2 inhibitor when compared with placebo for OA.[20] The other recent long-term trials of NSAIDs and COX-2 inhibitors for OA were focused on their comparative effectiveness and toxicity rather than their effect compared with placebo.[21,22] Most guidelines suggest that paracetamol should be used as first-line analgesia for knee OA. However, a number of studies suggest that oral NSAIDs are slightly more effective than paracetamol, at least in the short term.[23–27]

There is also a strong patient preference for NSAIDs compared with paracetamol. In one survey, 60% of participants with either OA or rheumatoid arthritis preferred NSAIDs to paracetamol.[28] In 2003, around half of a UK population sample with OA who had visited their GP were taking an NSAID or a COX-2 inhibitor.[29] A telephone survey in the USA found that of patients with OA taking paracetamol, naproxen, ibuprofen or diclofenac, 24, 30, 31 and 56%, respectively, reported these to be very helpful and that rates of long-term use were 33, 17, 21 and 19%, respectively.[30] In a pair of randomised controlled trials (RCTs), celecoxib was preferred by 53 and 50% of participants, compared with 24 and 32% preferring paracetamol.[31]

NSAIDs are easily available, either on prescription or over the counter, at a modest cost. However, in contrast to other conservative treatments for OA such as physiotherapy, exercise, paracetamol or glucosamine, oral NSAIDs are well documented to cause serious adverse effects in a substantial minority of those who use them.[13,16,32,33] One approach that might reduce these adverse effects, in particular gastrointestinal adverse effects, is to use topical NSAID preparations. These may achieve therapeutic concentrations in or around the knee with a lower overall dose and avoid any direct gastrointestinal effects, leading to an overall reduction in systemic adverse effects.[34] Although there is evidence that topical NSAIDs can have at least a short-term benefit, the role of topical NSAIDs in the treatment of OA remains poorly defined.[35,36]

Use of oral NSAIDs

Despite the risks of gastrointestinal, renovascular and respiratory adverse effects, oral NSAIDs are widely used for the symptomatic treatment of OA in older people.[37,38] In 2004, over 20 million prescriptions for oral NSAIDs, at a cost of over £250 million, were dispensed in England (http://www.dh.gov.uk/assetRoot/04/10/76/27/04107627.xls, accessed 8 December 2006). There are few data on the direct, indirect and intangible costs from using NSAIDs in older people; the personal and economic costs of managing adverse effects are, however, large. Around 40% of hospital admissions with upper gastrointestinal bleeding and 40% of associated deaths in older people are related to NSAID use.[39] It may be that around 2–4% of those taking oral NSAIDs have significant upper gastrointestinal complications annually, which is four times the background rate.[40]

Use of topical NSAIDS

Topical NSAIDs are also widely used: in England in 2005, topical NSAIDs accounted for 2.7 million dispensed prescriptions at a net ingredient cost of around £17 million (rubefacients accounted for 1.9 million dispensed prescriptions with a net ingredient cost of around £9.5 million) (http://www.ic.nhs.uk/pubs/prescostanalysis2005/pcaexcel/file, accessed 9 December 2006). Since several topical NSAID preparations are available over the counter, actual use is likely to be considerably higher than use based on prescription data. The prescription of topical NSAIDs is discouraged in a number of Primary Care Trusts in the UK, on grounds of poor evidence of their efficacy compared with oral NSAIDs or rubefacients; see, for example, Nottingham district-wide guidance (http://www.gedling-pct.nhs.uk/EasySite/lib/serveDocument.asp?doc=4170&pgid=4597, accessed 9 December 2006).

Effectiveness and safety of oral NSAIDs

There is good evidence for the short-term efficacy of oral NSAIDs in reducing pain due to OA.[41] There are few studies on the long-term effectiveness of NSAIDs for OA/knee pain;[42] the available evidence suggests that the benefits are less clear in long-term use.[17–19] Although there have been a number of recent large-scale trials of NSAIDs, with long term follow-up, these have been focused on the comparative risks of different NSAIDs and COX-2 inhibitors.[21,22] However, one study comparing celecoxib versus placebo over 24 weeks found that celecoxib produced a 20% reduction in WOMAC pain scores ($p = 0.008$).[20] The high incidence of gastrointestinal, renovascular or respiratory adverse effects from oral

NSAIDS is well documented;[43] gastrointestinal adverse effects are the most commonly recognised. One estimate for the proportion of older NSAID users admitted to hospital with gastrointestinal bleeding is 1.9%.[44] In one study, age over 75 years, history of peptic ulcer or gastrointestinal bleeding and a history of heart disease all increased the risk of upper gastrointestinal adverse effects.[45] A number of reviews have examined the comparative incidence of gastrointestinal adverse effects from different NSAIDs. Low-dose ibuprofen is the NSAID least likely to be associated with gastrointestinal bleeding.[32,46] Patients taking NSAIDs for more than 2 months may have an increased mortality rate from upper gastrointestinal bleeding of 1:1200.[47]

There is some concern about the renovascular effects of NSAIDs. In one study of an elderly population, NSAID users had higher levels of common laboratory markers of renal dysfunction;[48] in another study, adverse effects of NSAIDs on renal function showed that 6.8% of admissions with acute renal failure were associated with NSAID use.[49] Abnormalities in renal function are thought to occur in 1% of patients using NSAIDs.[50] In a meta-analysis of RCTs of NSAIDs, their use was associated with an average 5.0 mmHg [95% confidence interval (CI) 1.2 to 8.7 mmHg] elevation in mean blood pressure, which was significant in those taking antihypertensive drugs, consequently increasing the potential of hypertension-related morbidity, and possibly increasing the incidence of strokes by 67% and coronary heart disease by 15%.[51] Aspirin-induced asthma is present in 21% of asthmatic adults in a hospital clinical setting with a cross-sensitivity to ibuprofen in 98%, to naproxen in 100% and to diclofenac in 93% of patients.[52]

Since the present study was designed, there have been increased concerns about both oral NSAIDs and COX-2 inhibitors increasing the risk of coronary heart disease. Some COX-2 inhibitors have been withdrawn because of these risks. A meta-analysis of RCTs with indirect estimation of effects found an increased risk of vascular events from COX-2 inhibitors and diclofenac, but not naproxen. There was also a trend for ibuprofen to increase vascular events (rate ratio 1.51, 95% CI 0.96 to 0 2.37).[53] All the trials in this meta-analysis used high doses of these drugs: for ibuprofen, 800 mg, three times daily. Observational studies of the comparative incidence of these events in patients using different NSAIDs, where lower doses are likely to be used, found that ibuprofen use was not associated with serious coronary heart disease and it may lessen the cardioprotective effect of aspirin.[54,55]

Effectiveness and safety of topical NSAIDs

There are data to show that topical NSAIDs can achieve therapeutic concentrations in deep compartments.[56] Thus they could have pharmacological effects on peri-articular and intra-articular structures, and also through peripheral and central sensitisation.[36] An *ex vivo* study in patients with OA knee found that topical ibuprofen used in a high dosage (1125 mg of ibuprofen, 22.5 g of 5% ibuprofen gel per day per knee) achieves therapeutic concentrations in muscle and fasciae and low concentrations in synovial fluid and plasma.[57] After topical administration, the maximal plasma NSAID concentration is less than 15% of that achieved after oral administration.[34] A meta-analysis of studies using topical NSAIDs concluded that they were more effective than placebo ointments for chronic musculoskeletal disorders for up to 2 weeks of use.[40] Another meta-analysis considering longer periods of use for OA found that topical NSAIDs were no more effective than placebo after 3–4 weeks of use.[36] A meta-analysis of four trials found that diclofenac drops were an effective treatment for OA of the knee.[58] A major shortcoming of nearly all of these previous studies is the short follow-up. Older patients with chronic knee pain are likely to continue to have problems for many years; the risks and benefits of different medication need to be considered over a longer time frame than the short-term explanatory trials needed for licensing purposes.

The continued popularity of rubefacients, with no active ingredient (approximately 1.9 million prescriptions in 2005 in England http://www.ic.nhs.uk/pubs/prescostanalysis2005/pcaexcel/file, accessed 9 December 2006) supports the notion that patients' responses to topical NSAIDs may be partly mediated through the act of rubbing the affected part[59] and the patients' expectation of receiving a benefit.[60] There are some data suggesting that other active topical treatments, for example capsaicin, leeches, arnica, montana gel and topical glucosamine, may be efficacious for knee pain.[61–64]

A systematic review of RCTs of topical NSAIDs found no increase in adverse effects when topical NSAIDs were compared with placebo. When compared with oral NSAIDs, there was an excess

TABLE 1 *Placebo-controlled trials*

Type of adverse effects	No. of trials	No. of patients	Events/total		Relative risk (95% CI)
			Treatment	Placebo	
Local adverse effects	15	1734	53/949	48/785	1.0 (0.7 to 1.4)
Systemic adverse effects	16	1838	33/1002	14/836	1.7 (0.96 to 2.85)
Withdrawals due to adverse effects	10	1225	10/697	7/528	0.9 (0.4 to 2.1)

Adapted from Mason.[40]

TABLE 2 *Active controlled trials: topical versus oral*

Type of adverse effects	No. of trials	No. of patients	Events/total		Relative risk (95% CI)
			Topical	Oral	
Local adverse effects	2	443	19/243	4/118	3.0 (1.1 to 8.5)
Systemic adverse effects	3	764	82/408	87/356	0.8 (0.6 to 1.1)
Withdrawals due to adverse effects	3	764	19/408	24/356	0.7 (0.4 to 1.3)

Adapted from Mason.[40]

of local adverse effects in the topical group (8 versus 3)[40] (*Tables 1* and *2*).

Small, short-term RCTs of efficacy are not the best way of identifying adverse effects from NSAIDs.[40] The most frequently recognised adverse effects from oral NSAIDs are upper gastrointestinal problems. These are mediated through both local effects on the gastric mucosa and systemic effects.[65] Even if topical NSAIDs' main pharmacological effect is due to high local concentrations, there is still a risk of systemic adverse effects even with serum concentrations much lower than that achieved by oral NSAIDs.[34] Topical and oral NSAIDs would be expected to produce similar types of systemic adverse effects, with a lower incidence when topical NSAIDs are used. The occurrence of systemic NSAID adverse effects from topical preparations is unusual; local adverse effects are more common.[36,66] Topical NSAIDs can produce local irritation and rash.[40] These are typically minor and short-lived and resolve rapidly when treatment is discontinued. These local adverse effects generally have a minor health impact and they are not the focus of this report.

Oral versus topical NSAID effectiveness

A meta-analysis of RCTs shows that whereas topical NSAIDs are superior to placebo for OA, they are inferior to oral NSAIDs for pain and function in the first week of use, but that there is little difference over weeks 1–4.[36] A separate systematic review concluded that there was little evidence for a difference in efficacy between oral and topical NSAIDs.[40]

Role of patient preferences

For chronic disorders such as knee pain in older people where the evidence for substantial long-term benefits from any conservative treatments is not clear and where there is a range of potential treatments available, patient preferences may have an important part to play in selecting the most appropriate treatment option. Indeed, if a patient has a prior expectation of benefit or lack of benefit from a particular treatment approach, then this may influence both its effectiveness and the incidence of subjective adverse effects.

There are some data to show that patients with OA may opt for a less effective analgesic if it has fewer adverse effects.[67] The popularity of rubefacients and topical NSAIDs suggests that some patients with musculoskeletal pain may prefer a topical to an oral medication even if it is less effective. If patient preferences for route of administration of an NSAID do alter the effect of the treatment, this will need to be taken into account when considering NSAID use.

Health economics of oral and topical NSAIDs

Topical NSAIDs are substantially more expensive than their oral equivalent. The average net ingredient cost of all topical ibuprofen preparations dispensed in England in 2004–5 was £5.25; the equivalent cost for adult preparations of oral ibuprofen was £2.88 (http://www.ic.nhs.uk/pubs/prescostanalysis2005/final/file, accessed 9 December 2006). Based on using 10% ibuprofen gel with a defined daily dose for one knee of 1.5 g (see 'Defined daily doses of NSAIDs', on p. 26), the daily cost of topical ibuprofen for one knee is £0.09, whereas for 1200 mg of oral ibuprofen the daily cost is £0.15.[43] These daily costs may not be directly comparable since topical preparations may be used to treat more than one site of pain. A number of primary care organisations are actively discouraging GPs from prescribing topical NSAIDs as they have not been shown to be effective. Implicit in this is a desire to reduce prescribing costs; see, for example, guidance from Darlington (http://www.darlingtonpct.nhs.uk/documents/uploaded/LocalPrescribingGuide2004-05.pdf, accessed 9 December 2006. More explicit is the approach of the Scottish Auditor General, who has produced detailed recommendations on, and targets for, cost savings from reduced prescribing of topical NSAIDs (http://www.audit-scotland.gov.uk/publications/pdf/2003/03pf04ag.pdf, accessed 9 December 2006).

Prescribing costs are only part of the costs incurred from using oral and topical NSAIDs. Part of the rationale for using topical NSAIDs is that they should reduce the number of systemic NSAID adverse effects. One estimate of the overall cost to the NHS of managing gastrointestinal NSAID-related adverse effects alone was £251 million, of which £215 million was for co-prescriptions and £36 million for hospital admissions.[68] Estimates of the NHS and societal cost of managing other NSAID-related adverse effects, such as heart and renal failure and asthma, are less well acknowledged and rarely included in cost data for NSAID adverse effects.[69]

It is plausible that the routine substitution of topical for oral NSAIDs, although more expensive in cost per prescription, will produce an overall reduction of NHS and societal costs by reducing the costs of managing adverse effects. This could result in topical NSAIDs being considered a cost-effective alternative to oral preparations even if they are less effective. Hence a robust health economic analysis is needed to inform the decision whether or not to recommend the use of topical NSAIDs. Focusing on prescribing costs alone may be too simplistic.

Patient preference for oral or topical NSAIDs

Both topical and oral NSAIDs can be used for the treatment of knee pain in older people. If the combined effect of NSAID in the ointment, the act of rubbing and the patients' expectation of benefit produces an effect on pain and disability, and topical NSAID preparations have fewer adverse effects than oral preparations, then topical may be preferable to oral preparations as routine treatment for older patients with knee pain. There would be fewer adverse effects in those whose pain could be managed effectively by topical NSAIDs. Despite the shortage of evidence for the long-term effectiveness of any NSAID by any route, compared with placebo or paracetamol, for treating knee pain or OA in older people, they are still very widely used. Hence, this research is set in the context that there is a commitment to use oral NSAIDs, making them the standard against which alternatives should be measured. Measuring the balance of risk and benefits of the two routes of administration is an important research question; even if both oral and topical NSAIDs are ineffective in the long term, they are likely to continue to be widely used.

In this report, we are seeking to answer the following question:

> "Should GPs advise their older patients with knee pain to use topical or oral NSAIDs?"

In this study, we compare advice to use alternative routes of administration rather than evaluate the efficacy or effectiveness of topical or oral NSAIDs. To be directly applicable in clinical practice, patient preferences for route of administration also need to be considered.

Which NSAID?

There are 24 oral NSAID or COX-2 inhibitor compounds marketed in the UK (aceclofenac, acemetacin, celecoxib, dexibuprofen, dexketoprofen, diclofenac sodium, diflunisal, etodolac, etoricoxib, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, lumiracoxib, mefenamic acid, meloxicam,

nabumetone, naproxen, piroxicam, sulindac, tenoxicam and tiaprofenic acid). Four of these (diclofenac, ibuprofen, ketoprofen and piroxicam) are also available as topical preparations. One additional compound (felbinac) is available just as a topical preparation.[43] There are also 12 rubefacients and capsaicin preparations available on prescription. For this study, we wanted to test the effect of advising patients to use either a topical or an oral route of delivery for NSAIDs. By asking participants to preferentially use different preparations with the same active ingredient we were able, to some extent, to control for any differences between NSAIDs and to be assured that we were primarily comparing the route of administration.

Ibuprofen is the best choice of compound when comparing topical and oral NSAIDs:

1. It is available in both oral and topical forms.
2. There are no obvious differences in effectiveness between NSAIDs for the treatment of knee OA.[70]
3. A meta-analysis of the risk of gastrointestinal side-effects found that low-dose (≤1200 mg/day) ibuprofen had the lowest risk compared with other NSAIDs.[32]
4. Ibuprofen is one of the most commonly dispensed NSAIDs, both orally and topically. In 2004 there were over four million and over one million prescriptions dispensed for oral and topical ibuprofen, respectively, in England (http://www.dh.gov.uk/assetRoot/04/10/76/27/04107627.xls, accessed 9 December 2006). These represent 25% of oral and 22% of topical NSAID prescriptions, respectively. Ibuprofen is also available in oral and topical formulations as an over-the-counter product.
5. At the time that the study was designed, many people believed that COX-2 inhibitors were safer than traditional NSAIDs, in particular that the reduced risk of upper gastrointestinal bleeding meant that they should be used in preference to traditional NSAIDs for older people. Reviewing the available literature, we concluded that the risk of upper gastrointestinal bleeding was likely to be similar for low-dose ibuprofen (≤1,200 mg/day) and COX-2 inhibitors, and that there were grounds to be concerned about possible increased risk of cardiovascular events in patients taking COX-2 inhibitors.[71] As the study was concluding, concerns were also raised about a possible increase in cardiovascular events owing to a number of traditional NSAIDs, including ibuprofen.[53]

Chapter 2

Aims, objectives and overview of the study

Aims

The original research question proposed by the HTA Programme was the following:

> "What is the long-term cost-effectiveness of topical NSAIDs versus oral NSAIDs in osteoarthritis?"

In our original proposal, we posed the following research question:

> "Are topical and oral ibuprofen equally effective for the treatment of chronic knee pain in older people?"

We subsequently refined this to take into account the comparative effectiveness of topical NSAIDs, their cost-effectiveness and patient preferences. Therefore, the overall aim of the Topical or Oral IBuprofen (TOIB) study was more specific and applied:

> "To determine whether GPs should advise their older patients with chronic knee pain to use topical or oral NSAIDs."

To achieve this aim, we set the following objectives.

Objectives

The objectives were as follows:

Effectiveness:
- to compare the effect on pain and disability of GPs' recommendations to (preferentially) use either topical or oral ibuprofen.

Adverse effects:
- to develop a measure of minor NSAID adverse effects
- to compare the rate of minor and major adverse effects as a result of preferentially using topical or oral ibuprofen
- to explore participants' perceptions of NSAID adverse effects.

Health economic evaluation:
- to compare the societal costs and benefits of preferentially using topical or oral ibuprofen, in terms of the impact that the route of administration has upon the NHS, the patient and other service providers
- to compare the cost-effectiveness of preferentially using topical or oral ibuprofen and examine how this is influenced by treatment compliance
- to determine the predicted long-term cost-effectiveness of preferentially using topical or oral ibuprofen on the likelihood and extent of major and minor adverse effects.

Patient preference aims:
- to evaluate the impact of patient preferences on the comparative effectiveness and cost-effectiveness of topical or oral ibuprofen
- to explore the reasons for patient preferences for topical or oral NSAIDs.

Overview

To achieve these objectives, we conducted a number of linked studies (*Figure 2*):

1. a Delphi study to develop a definition of minor adverse effects
2. an RCT
3. a patient preference study (PPS)
4. a health economic evaluation using data from the PPS and the RCT
5. a parallel qualitative study exploring the effect of patient preference and attitudes and behaviours about adverse effects.

These studies stand as individual pieces of work and also contribute to addressing our overall aim of determining whether GPs should advise their older patients with chronic knee pain to use topical or oral NSAIDs.

As the final interpretation of the results of this study depends on the balance between risks and benefits of the two routes of administration, an important first step was to develop a set of criteria for defining minor clinical adverse effects. This process is described in detail in Chapter 3. We used these criteria to measure the occurrence of adverse effects during follow-up. Our primary effectiveness analysis is based on the RCT, with the data from the PPS being used to assess the effect

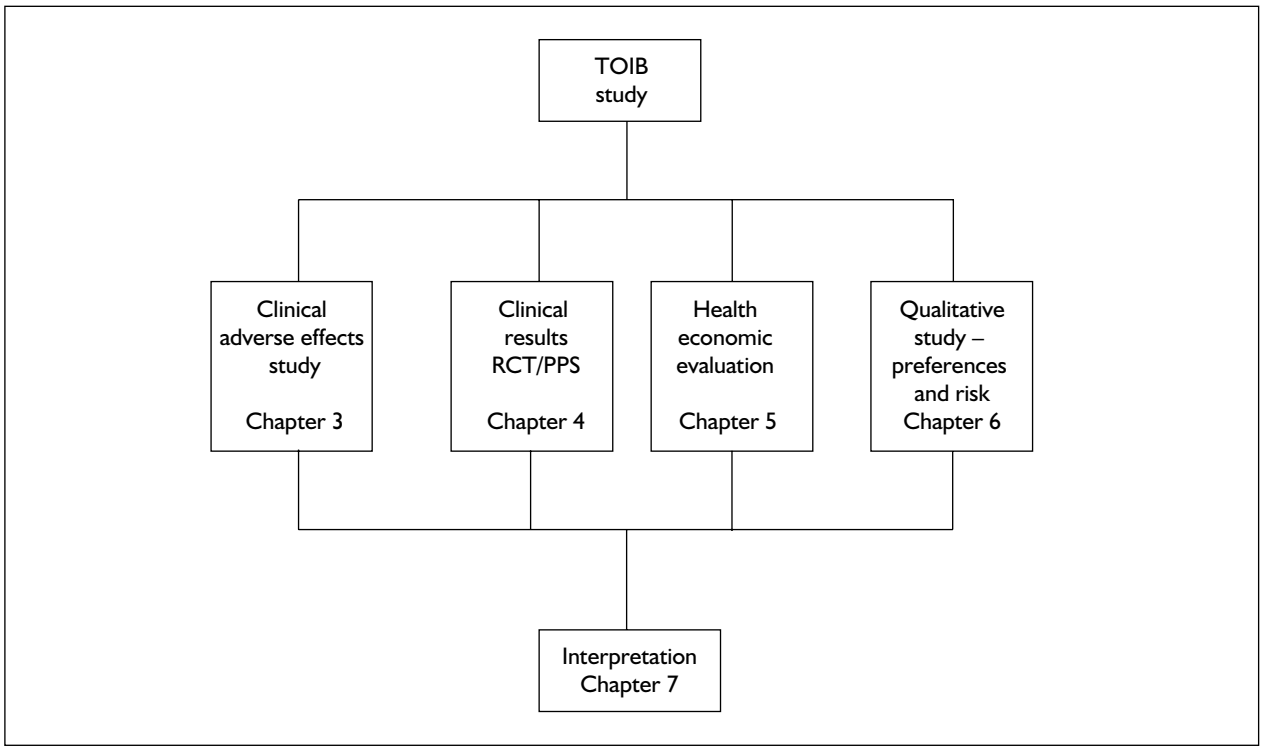


FIGURE 2 *Overall structure of the study*

of patient preferences on outcome. The economic analysis makes use of data from both the questionnaire and examining general practice records; data are presented separately for the RCT and PPS and for short-term (12 months) and longer-term (24 months) follow-up. Finally, the data from qualitative studies of patients' beliefs about adverse effects and their reasons for different treatment preferences are used to inform the interpretation of the RCT and PPS results. Each part of the study is presented as a separate chapter; a summary of the compiled results and implications of all our findings is presented in the final chapters.

Chapter 3

Defining minor clinical adverse effects

Background

Defining and measuring minor clinical adverse effects is crucial to the interpretation of this study. NSAIDs are well known to have a wide range of systemic adverse effects. However, there is little consistency in how these have been reported in previous studies. For the TOIB study we defined major adverse effects as either death or an unplanned hospital admission. We also wanted a measure of less serious adverse effects to inform a proposed risk–benefit analysis. At the study design stage we selected a number of clinical outcomes that measured possible NSAID-related adverse effects in each of three groups: gastrointestinal, renovascular and respiratory. However, we were unaware of any suitable definitions that would allow us to conclude that a minor adverse effect was present. We therefore carried out a Delphi study with the aim of developing an agreed definition of minor clinical adverse effects from NSAIDs for use in the TOIB study.

Method

Delphi study of GPs

The Delphi technique is a consensus building process. It involves a series of sequential questionnaires or 'rounds', combined with feedback, that seeks to gain the most reliable consensus of opinion of a group of experts.[72] In this case, the problem was defining minor clinical adverse effects that occur with NSAID use. We aimed to achieve a consensus about levels of clinical change that would trigger advice to change medication use. The main areas to achieve consensus were as follows.

Gastrointestinal

NSAIDS work by inhibiting the action of cyclooxygenase, which in turn inhibits prostaglandin synthesis. NSAIDs can cause gastrointestinal damage by both local and systemic effects, but the systemic effects are more important.[73] Inhibition of prostaglandin synthesis in the stomach leads to decreased secretion of protective mucus and bicarbonate, and also increased acid secretion. Mucosal irritation, ulceration and bleeding may result. We assessed presence of gastrointestinal adverse effects using participant self-report and blood tests.

Dyspepsia

This is one of the commonest reported adverse effects of NSAIDs. However, it is difficult to define clinically or to measure accurately.[74] We asked about frequency of indigestion, a general term which covers a range of abdominal symptoms, over the last 3 months, using five categories from 'no days' to 'every day'.

Iron deficiency or iron deficiency anaemia

Gastric ulceration and bleeding are potentially serious adverse effects of NSAIDs, but in addition to frank bleeding, insidious blood loss may occur.[75] To assess this, we measured haemoglobin (Hb) and ferritin. These were tested at study entry, 12 months and end of study follow-up; the results of any blood test carried out as part of normal clinical care during the study period were also monitored. In this part of the study, we determined the clinically important changes in Hb and ferritin.

Renovascular

In the kidney, prostaglandins are involved in distribution of blood flow, maintenance of the glomerular filtration rate and sodium chloride transport.[76] Reduced prostaglandin production due to NSAID use results in reduced blood flow to the kidney and sodium retention. Hyperkalaemia can also occur. A common result of this is fluid retention; symptomatic oedema occurs in about 5% of NSAID users, but is usually of little clinical concern. More serious effects include a rise in blood pressure and exacerbation of heart failure. One meta-analysis of RCTs estimated that NSAIDs increased mean blood pressure by 5 mmHg (95% CI 1.2 to 8.8).[51] Several studies have shown an increased risk of development of, or admission with, heart failure related to use of NSAIDs.[77,78] Prostaglandins in the kidney are particularly important in maintaining renal perfusion when it is compromised by dehydration, renal or cardiovascular disease, and in the elderly. People with these conditions may be more at risk from renal effects of NSAIDs, and acute deterioration in renal function may occur.[79] More subtle changes in renal function are also common, especially in

the elderly.[48] We assessed the presence of renovascular side effects using clinical examination, medical record examination and blood tests.

Hypertension
We measured blood pressure at study entry, 12 months and end of study follow-up, and searched participants' medical records for any new diagnosis of hypertension and changes in medication during the study period.

Heart failure
At the end of the study, we searched practice records for new diagnoses of heart failure during the follow-up period.

Deteriorating renal function
We measured creatinine at baseline, 12 months and end of study follow-up, and collected the results of any test carried out as part of normal clinical care during the study.

Respiratory
Aspirin-induced asthma is a recognised adverse effect of NSAIDs.[80] One population survey found the prevalence of symptomatic aspirin-induced asthma in adults was 1.2%.[81] On provocation around 20% of asthmatic adults show sensitivity to aspirin and cross-sensitivity exists to other commonly used NSAIDs.[52] The cause of aspirin-induced asthma is thought to be excessive production of leukotrienes due to the accumulation of prostaglandin precursors in the lung.[82] We assessed the presence of respiratory adverse effects using clinical examination and medical record data.

Peak flow
We measured peak flow at baseline 12 months and end of study follow-up.

New diagnosis of asthma or chronic obstructive pulmonary disease
At the end of the study, we searched practice records for new diagnoses of asthma or chronic obstructive pulmonary disease (COPD), since the symptoms overlap considerably.

Use of medication
We collected information on new prescriptions of either a beta-2 agonist or a steroid inhaler during the follow-up period.

While both oral and topical NSAIDs may cause skin reactions, these were not specifically included in the information collected during follow-up. Mechanisms for these reactions are likely to differ between oral and topical NSAIDs; severe skin reactions are uncommon with both routes of administration. Participants were asked about any reason for stopping or changing treatment.

For our final analysis, we needed to define when these data indicated the presence of a minor adverse effect.

Participant identification

Members of the Primary Care Rheumatology Society attending their 2004 annual conference were approached to become the expert group for the Delphi consultation. This is a society for GPs with a special interest in musculoskeletal disorders (http://www.pcrsociety.org.uk/, accessed 9 December 2006). An expert group in a Delphi study should have particular expertise in the topic being discussed. Our group consisted of GPs with a special interest in musculoskeletal problems. They had expertise in the management of such problems in a primary care setting, and were therefore more suitable than a group of specialist rheumatologists dealing with patients in secondary care who would not resemble our study population.

The questionnaire

We have discussed above the range of potential NSAID adverse effects monitored during follow-up of the RCT and PPS. The Delphi questionnaire was developed to explore expert opinion about acceptable and unacceptable levels of change in these areas. The questions used are summarised in *Table 3* and shown in full in Appendix 1.

Administration of questionnaire

Figure 3 shows the cycle of events needed to occur before consensus can be achieved.

We sent an initial questionnaire with an explanatory letter by post, with the conference materials, to all PCR members planning to attend the conference. Members who had not returned the questionnaire before the conference were invited to participate at the conference. We asked participants to respond to questions about adverse effects to determine the level of severity at which the participant would advise a typical patient to discontinue NSAID treatment. In some questions, respondents were asked to rate their agreement with a statement on a scale of one to nine, or to suggest a value of a parameter at which they would discontinue treatment. Some questions also asked for a level at which the participant would be happy to continue treatment. Some categorical

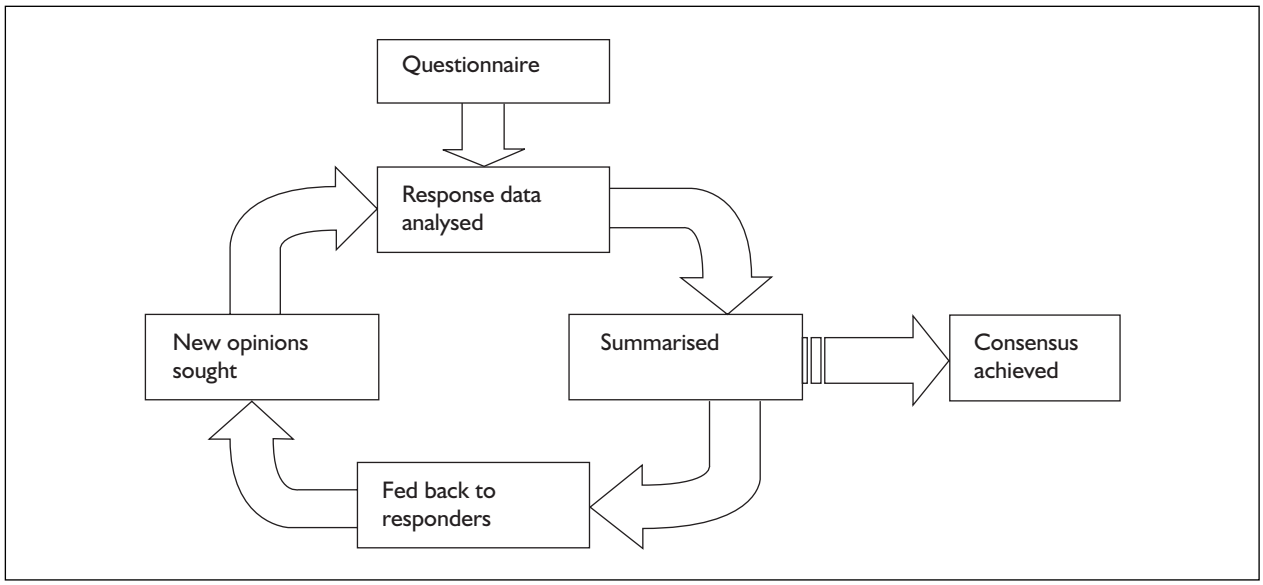


FIGURE 3 *Consensus cycle for the Delphi study*

questions were also included. Free text questions allowed participants to give comments on the issues raised.

The answers to the first questionnaire were summarised and, following this, each participant was sent a second-round questionnaire. This was identical with the first except that participants were given their previous response to each question and a summary measure of responses to each question as feedback. The summary measures were the median and interquartile range for rating scale questions, the proportion choosing each category for categorical questions or the mean and standard deviation (SD) for laboratory values. Comments were also summarised and the three most common comments in each section were fed back to participants. The second-round questionnaire was initially sent by email to all participants who had provided an email address; the others were sent by post. Two postal reminders were sent. The aim was to keep contacting respondents until a consensus was achieved (*Table 3*).

Definition of consensus

This varied according to the type of question as follows:

1. Rating scale of one to nine for agreement with a statement.
   (a) The median score and interquartile range were calculated.
   (b) Consensus was considered to have been achieved if the interquartile range was no more than one mark above or below the median.
   (c) For these questions only, there was a separate issue of **agreement** with the statement. We defined this as a median score of seven, eight or nine. For example, if the median score was six with an interquartile range of five to seven, this would constitute consensus, but not agreement.
2. Choice of category.
   (a) The percentage of participants opting for each category was calculated.
   (b) Consensus defined as 80% of the participants choosing one category.
3. Stating a value for a parameter.
   (a) The mean and SD of the suggested values were calculated
   (b) Consensus for these questions was considered to have been reached when the SD was within a predefined range (±1 g/dl for Hb estimates; ±20 mmol/l for creatinine).

Results

Participants and response rate

Questionnaires were returned by 62/95 (65%) of those attending the conference. Fifty-two participants responded in both the first and the second rounds. After second rounds, consensus had been achieved in 17 of the 22 questions that did not ask for free text comments. The researchers judged that another round was

TABLE 3 *Summary of questions in Delphi consultation*

Subject of questions	Question type	Description
Level of indigestion symptoms Drop in serum ferritin Rise in systolic blood pressure Rise in diastolic blood pressure Rise in serum creatinine	Categorical	Select category at which would stop NSAIDs
Increase in indigestion symptoms by one category Increase in indigestion symptoms by more than one category Serum ferritin below normal range New diagnosis of hypertension Control of existing hypertension worsens New diagnosis of heart failure Drop in peak expiratory flow rate of 15% New diagnosis of asthma New diagnosis of chronic obstructive pulmonary disease Additional treatment needed for asthma/COPD	Rating scale 1–9	Level of agreement with statement about when to stop NSAIDs
Values of Hb for men and women above which would continue Values of Hb for men and women below which would stop Drop in Hb above which would stop Value of serum creatinine below which would continue Value of serum creatinine above which would stop	Values	Suggest value for laboratory test at which would stop NSAIDs or would be happy to continue them
Indigestion Evidence of occult bleeding Hypertension Renal insufficiency or sodium retention Bronchospasm Any other comment	Free text	Text box for opinions

unlikely to result in important changes to the level of consensus.

Analysis

Summary responses to the first and second round are shown in *Tables 4–6*. Consensus was achieved for questions on the level of indigestion symptoms and increase in indigestion symptoms, Hb levels, ferritin below normal range, worsening of existing hypertension, rise in diastolic blood pressure by 10 mmHg, creatinine values, new diagnosis of heart failure, peak flow rate drop of 15%, new diagnosis of asthma and additional treatment needed for existing asthma. Consensus was not reached for a drop in ferritin, new diagnosis of hypertension, rise in systolic blood pressure, rise in creatinine or a new diagnosis of chronic obstructive pulmonary disease. For this last question, there was also poor agreement with the statement (median score 6).

Free text comments made by the participants indicated that they did not routinely monitor patients on NSAIDs for adverse effects, that the balance of benefit to risk had to be taken into account, that other causes of some of the potential adverse effects should be sought (for example, a drop in Hb could be related to occult malignancy) and that they had difficulty interpreting ferritin levels. Some also commented that they might prefer to co-prescribe to treat some of the adverse effects, rather than stop the NSAIDs if they were effective for an individual patient.

Discussion

It was possible to achieve a consensus among GPs on the severity of a range of minor adverse effects to NSAIDs that would lead to advice to stop the medication. Similar methods were used by Cabral and colleagues to develop a rating scale for severity of rheumatoid arthritis from medical records.[83] Defining individual minor adverse effects allows a more detailed picture of the adverse effect burden to be built up, which has not been possible in previous studies. This may allow finer distinctions to be drawn between different NSAIDs and routes of administration than have been possible before.

One drawback of the Delphi process is that it did not include the opinions of patients. Patients are likely to view the importance of NSAID adverse

TABLE 4 *Gastrointestinal adverse effects*

Question	Summary measure	Round 1	Round 2
Level of reported indigestion symptoms	% responders for each option		
A few days		10	2
More than occasionally, but fewer than half the days		70	92[a]
Most days		20	6
Every day		0	0
An increase in one category for indigestion (scale 1–9)	Median and interquartile range	8 (7–9)	8 (7–8.25)[a]
An increase in more than one category for indigestion (scale 1–9)	Median and interquartile range	9 (8-9)	9 (9–9)[a]
Hb for male patient above which would continue treatment	Mean and SD	12.5 (0.7)	12.5 (0.5)[a]
Hb for female patient above which would continue treatment	Mean and SD	11.6 (0.6)	11.6 (0.4)[a]
Hb for male patient below which would stop treatment	Mean and SD	11.3 (0.9)	11.3 (0.7)[a]
Hb for female patient below which would stop treatment	Mean and SD	10.6 (0.7)	10.6 (0.4)[a]
Fall in Hb at which would stop treatment	Mean and SD	1.6 (0.5)	1.6 (0.4)[a]
Drop in ferritin at which would stop treatment	% responders in each category		
5 μg/l or less		6	6
10 μg/l		30	23
20 μg/l		26	23
30 μg/l or more		39	48
If the ferritin falls below normal range (scale 1–9)	Median and interquartile range	8 (6–9)	8 (7–9)[a]

[a] Consensus achieved.

effects differently to doctors. It is possible that a symptomatic adverse effect such as indigestion would be regarded as much more important by a patient than an asymptomatic one such as a rise in blood pressure or creatinine. We have explored patients' opinions on NSAID adverse effects in a separate qualitative study using in-depth interviews of study participants (Chapter 6).

Composite measure of adverse effects for use in TOIB trial

Using these data, we were able to develop a composite measure of minor adverse effects for use in the TOIB trial. Items were included if our experts had reached consensus and, for the rating scale questions, also indicated agreement. Rise in creatinine was included because it had been very close to consensus (74% agreement on a rise of 20 mmol/l) and was felt by the study team to be important clinically. For similar reasons, rise in systolic blood pressure was also included; 55%, an overall majority, agreed on a rise of 20 mmHg. Questions concerning continuing treatment rather than stopping it (questions 5a, 5b and 16) were not used for the minor adverse effect measure. It is possible that within any domain (gastrointestinal, renovascular or respiratory) these adverse effects will cluster within the same individual. For example, one participant might have a reduced Hb concentration and also have increased indigestion. For this reason, for our composite outcome measure we report the presence of individual adverse effects and the presence of one or more minor adverse effects in each domain. Finally, we report the total number of people suffering from one or more adverse effect in any domain. This is appropriate since each minor clinical adverse effect (i.e. any adverse effect that does not lead to an unplanned hospital admission or death) has been defined as something that would lead the GP to consider changing treatment. Thus multiple events such as these would not achieve a greater clinical

TABLE 5 *Renovascular adverse effects*

Question	Summary measure	Round 1	Round 2
If there is a new diagnosis of hypertension (scale 1–9)	Median and interquartile range	5 (4–8)	6 (5–8)
If control of existing hypertension worsens (scale 1–9)	Median and interquartile range	7 (5–8)	7 (6–8)[a]
Rise in systolic blood pressure	% responders in each category		
5 mmHg or less		2	0
10 mmHg		30	26
15 mmHg		20	17
20 mmHg		42	55
25 mmHg		3	2
30 mmHg or more		3	0
Rise in diastolic blood pressure	% responders in each category		
5 mmHg or less		15	4
10 mmHg		56	90[a]
15 mmHg		21	6
20 mmHg		8	0
25 mmHg		0	0
30 mmHg or more		0	0
Creatinine value below which would continue treatment	Mean and SD	129 (17)	128 (11)[a]
Creatinine value above which would stop treatment	Mean and SD	154 (22)	152 (13)[a]
Rise in creatinine at which would stop treatment	% responders in each category		
10 mmol/l or less		9	4
15 mmol/l		28	17
20 mmol/l		50	74
25 mmol/l		5	4
30 mmol/l or more		9	0
New diagnosis of heart failure (scale 1–9)	Median and interquartile range	8 (7–9)	8 (8–9)[a]

[a] Consensus achieved.

TABLE 6 *Respiratory adverse effects*

Question	Summary measure	Round 1	Round 2
Reduction in peak flow rate of at least 15% (scale 1–9)	Median and interquartile range	8 (6–8)	8 (7–8)[a]
New diagnosis of asthma (scale 1–9)	Median and interquartile range	8 (7–9)	8 (7–9)[a]
New diagnosis of COPD (scale 1–9)	Median and interquartile range	6 (4–7)	6 (5–7)[b]
Additional treatment needed for asthma/COPD (scale 1–9)	Median and interquartile range	7 (6–8)	7 (7–8)[a]

[a] Consensus achieved.
[b] Actual 25th percentile 4.75, therefore consensus not reached.

importance, although they would increase the harm to the individual (*Table 7*).

We carried out this Delphi study after the start of participant recruitment. For dyspepsia our experts set a more stringent criterion for stopping NSAIDs than we had set as our criterion for study entry. We therefore used the inclusion criteria originally set for the study for participant recruitment and used the Delphi criteria for our outcome analysis.

TABLE 7 *Definition criteria for adverse effects*

System	Measure	Agreed change
Gastrointestinal	Haemoglobin	Hb <11.3 g/dl (male) Hb <10.6 g/dl (female) Fall in Hb ⩾1.6 g/dl
	Ferritin	Ferritin below lower limit of normal for local laboratory
	Dyspepsia	Indigestion more than occasionally, but fewer than half the days Increase in indigestion by one or more category[a]
Renovascular	Creatinine	Creatinine ⩾152 mmol/l Increase in creatinine ⩾20 mmol/l
	Blood pressure	Increase systolic blood pressure ⩾20 mmHg Increase diastolic blood pressure ⩾10 mmHg
	Heart failure	New diagnosis of chronic in heart failure
Respiratory	Asthma	New diagnosis of asthma Increase in treatment required for asthma or COPD[b] 15% fall in peak flow

[a] A few days; more than occasionally, but fewer than half the days; most days; every day.
[b] Measured in this study by upgrading of class of drugs, not increase in amount of drugs.

Conclusion

This approach has allowed us to develop a set of criteria for defining and reporting minor NSAID adverse effects. Using this in the TOIB study allows us to report these adverse effects in a systematic manner that is firmly grounded in routine general practice.

Chapter 4

The randomised controlled trial and the patient preference study

Introduction

Although the evidence of long-term effectiveness for either topical or oral ibuprofen is weak, they are both well established treatments for chronic knee pain in older people.[84] Therefore, rather than seeking to show that topical ibuprofen is either more or less effective than oral treatment, we sought to provide information useful for GPs to inform their management of patients consulting with chronic knee pain, **given that oral NSAIDs are an established treatment for OA**. Many people with knee pain will self-medicate with topical or oral ibuprofen, which is freely available in pharmacies and supermarkets.[85] These patients may not be in contact with the health service for knee pain because they are satisfied with self-medicating, finding it more convenient to obtain painkillers off prescription for occasional use, or may be dissatisfied with the advice they have received. We hypothesised that people consulting with chronic knee pain were likely to have more troublesome pain requiring more frequent treatment. For this reason, our participants were all people who had sought care for their knee pain from their GP and still had knee pain. Originally we restricted the study to patients aged 65 years or more, but we reduced the age limit to 50 years when it became apparent that the required sample size would be difficult to obtain. This lower age limit matches that used in the ACR clinical diagnostic criteria for OA, and has been used in a number of previous studies of knee pain.[5,6,86]

In practice, in a primary care consultation, prescribing decisions are based not only on GPs' beliefs about the effectiveness, side-effects and costs of treatment but also on patients' preferences.[87] Patients' preferences for topical or oral preparations for knee pain may be grounded in past experience, marketing by the pharmaceutical industry and folk models of illness.[48,88–90] The very obvious differences in the routes of administration between topical and oral NSAIDs mean that patients' preferences may have sizeable influences on the perceived effectiveness of the two treatments of knee pain. Understanding these effects will provide important information to inform the discussion between GPs and their patients on administration route and choice of treatment. For this reason, rather than simply asking participants' preferences[91] we did a patient preference study using the Brewin and Bradley model (*Figure 4*).[92] In an open study of this nature, it is impossible to blind either the participant or his/her GP as to which preparation is being used, making it plausible that participants' preferences could affect outcomes. This could be due either to participants using more of their preferred medication or a greater expectancy of benefit from their preferred route of delivery.[93] In the context of this study, one might expect positive effects on subjective outcomes such as pain or disability and negative effects on subjective outcomes such as dyspepsia.[93] This reflects what will happen in routine general practice.

This research sought to test the following hypotheses:

- That older patients advised to use topical or oral NSAIDS for chronic knee pain have similar levels of knee-related pain and disability after 12 months.
- That older patients using topical NSAIDs for chronic knee pain have fewer minor adverse effects than those using oral preparations.
- That there is a difference in the balance of risks and benefits between oral and topical NSAIDs when used for the treatment of knee pain in older people.

In addition, we explored how the preferences of older patients for topical or oral NSAIDs for chronic knee pain could affect their response to treatment.

Next we describe the RCT and the PPS: the recruitment and follow-up of all participants, the analysis of both and finally the health economic analysis.

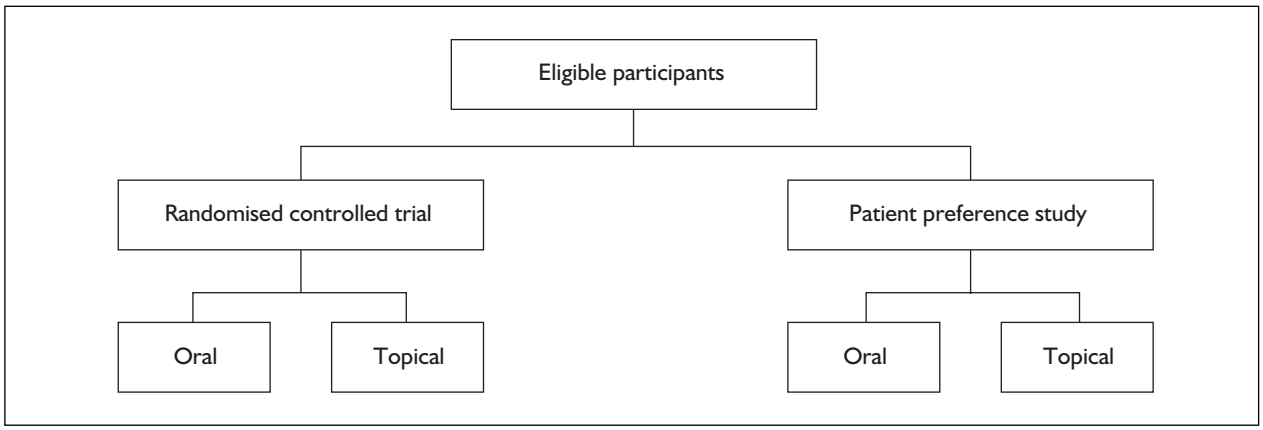


FIGURE 4 *Overall study design*

Method

Study sites/settings

Our participants were recruited by practices from the Medical Research Council General Practice Research Framework (GPRF).[94] We sought to recruit practices that were nationally representative in terms of region and deprivation, as measured by the Jarman index,[95,96] and type of locality (inner city/urban/suburban/rural). The Jarman index may not be the most appropriate measure to assess deprivation but, unlike some other measures, it is available for all parts of the UK. We evaluated the effectiveness of our sampling strategy for our English practices using the Index of Multiple Deprivation for their location. This index is a super-output area level measure of multiple deprivation and is made up of seven indices: income, employment deprivation, health deprivation and disability, education, skills and training, barriers to housing and services, crime and living environment (http://www.communities.gov.uk, accessed 9 December 2006). Social class was categorised using the Standard Occupational Classification System, which identifies 10 occupational groups ranging from managerial/professional to no paid work (Office of National Statistics, http://www.statistics.gov.uk/methods_quality/ns_sec/downloads/SOC2000.doc, accessed 8 December 2006). Ethnic groups were based on those used in the 2001 UK census. Within each practice, recruitment was carried out by a practice-based research nurse who had received a full day of training on study procedures from the study team.

Pilot sites

We piloted the study in two practices. There were no significant changes in the study protocol between the pilot practices and the main study. For this reason, we have included data from one pilot practice in our main analysis. Participants from the other practice were not included in the quantitative analysis because several of them had been included in our initial exploratory qualitative study.

Participant recruitment

Identifying older people who had consulted with knee pain from general practices was not straightforward. In the background section, we described the overlap between the diagnoses of knee pain and OA of the knee. The Read code system that is used by most general practice computing systems in the UK allows the content of consultations to be coded. However, there are many codes that might identify older patients consulting with knee pain; these include specific knee OA codes and also generic knee pain codes as either symptoms or diagnoses. Few GPs have had specific training in coding consultations and their coding may therefore lack consistency. Hence, any search of general practice computerised records needed to set very broad parameters to identify those who had consulted for knee pain. Inevitably such a search identified many people who did not have, or who had not consulted for, chronic knee pain. Patients with a long history of knee pain are also less likely to have consulted recently than those with a relatively short history.[97] Furthermore, it may be that for many older people who sought advice for chronic knee pain a diagnosis was not specifically coded within their medical record. For example, patients who had been using NSAIDs for knee pain might originally have been given these for another problem, or have been using them for many years before coding of consultations was commonplace.

To maximise recruitment, we used three approaches:

1. Searching the electronic medical records within general practices for patients aged 50 years or over who had consulted with OA or knee/leg pain in the preceding 5 years.
2. Searching electronic prescribing databases for all patients aged 50 years or over who received a prescription for oral/topical NSAIDs or a rubefacient over the preceding year.
3. Asking GPs to notify the practice research nurse when potentially eligible patients consulted during the study recruitment period.

Computer searches

When using patients' data held by their GP without the patients' explicit consent, it was essential that systems were in place to ensure that access to personal information was kept to an absolute minimum.[98,99] In particular, it is usually unacceptable for researchers from outside the NHS to have access to patient-specific data without explicit consent, or for NHS staff to access patient-specific data unnecessarily. In addition, it was important to avoid approaching those who explicitly did not wish to be involved in such research, or who might find an unsolicited approach distressing. To address these points, we used a system that was as far as possible automated, with some manual checks by staff from participating practices.

After training, the practice-based research nurses searched the practice computer using MIQUEST.[100] This program was obtained from the National Health Service Information Authority; it searches nearly all general practice software in current use. We used MIQUEST to select patients aged over 50 years who either had a diagnosis of OA or knee pain recorded within the last 5 years, who had consulted about knee pain in the last 3 years or who had received a prescription for NSAIDs or a rubefacient over the previous 12 months. Read code version 2 was used for all search terms, except for practices using Egton Medical Information Systems (EMIS) (http://www.emis-online.com/, accessed 9 December 2006) computer software, which has a separate coding system for medications based on chapters of the British National Formulary (BNF). All the records for patients aged 50 years or over were searched. Potential participants with any of the codes in *Table 8* in their record over the periods specified above were selected.

The output from this search contained the patients' names and addresses, with some demographic data. The practice-based research nurse downloaded the information onto a study laptop that generated study identification numbers and printed personalised approach letters and participant registers using a bespoke software program. After printing the study paperwork, all patient data were automatically removed from the study computer. Patient-specific data were released to the study team only after explicit consent had been obtained from potential participants.

Before any approach letters were sent, the practices checked the list for patients who had explicitly requested not to be approached about participating in research. In addition, the practices screened the list to identify patients whom it would be inappropriate to approach, for example those with severe mental illness, advanced dementia or a terminal illness.

TABLE 8 *Codes used for practice computer searches*

Code	Definition
Read code	
N05 …	Osteoarthritis (and [allied disorders])
N06 …	Other and unspecified joint disorder
N09 …	Other and unspecified mechanical joint disorder
1M10	Knee pain
Drug read codes	
j2 …	Non-steroidal anti-inflammatory drug
jA …	Cyclooxygenase-2 inhibitor drug
ja …	Rubefacients and other topical
EMIS drug codes (BNF chapter based)	
10.1.1	Non-steroidal anti-inflammatory drugs
10.3.2	Rubefacients and other topical anti-rheumatics

This method for approaching potential participants minimised access to patient records, ensured that all patient-identifiable data remained within the practice until explicit consent had been given for it to be released to the study team and automated the production of study paperwork.

Notification of incident cases

During the study recruitment period, GPs were asked to notify the research nurse directly of any patients aged 50 years or over consulting with knee pain.

Participant identification and selection

Starting from the list of potential participants generated by our computer search, we used a five-stage recruitment process that identified those who were troubled by knee pain, met our consultation criteria, were interested in taking part in the study and met our safety criteria. (*Figure 5*).

1. The practice screened the potential list of participants to identify those who should not be approached using the predetermined inclusion and exclusion criteria (*Tables 9* and *10*).
2. An initial approach questionnaire (IAQ) was used to confirm the presence of knee pain and ascertain interest in the study.
3. A first nurse assessment (FNA) confirmed knee pain eligibility criteria: safety criteria were assessed and blood taken for baseline laboratory tests.
4. A medical assessment (MA) by the GP confirmed that the potential participant met safety criteria and their knees were examined.
5. The study entry assessment (SEA) confirmed eligibility: consent and baseline participant data were collected.

From the FNA onwards, potential participants in the practices recruiting to both the RCT and the

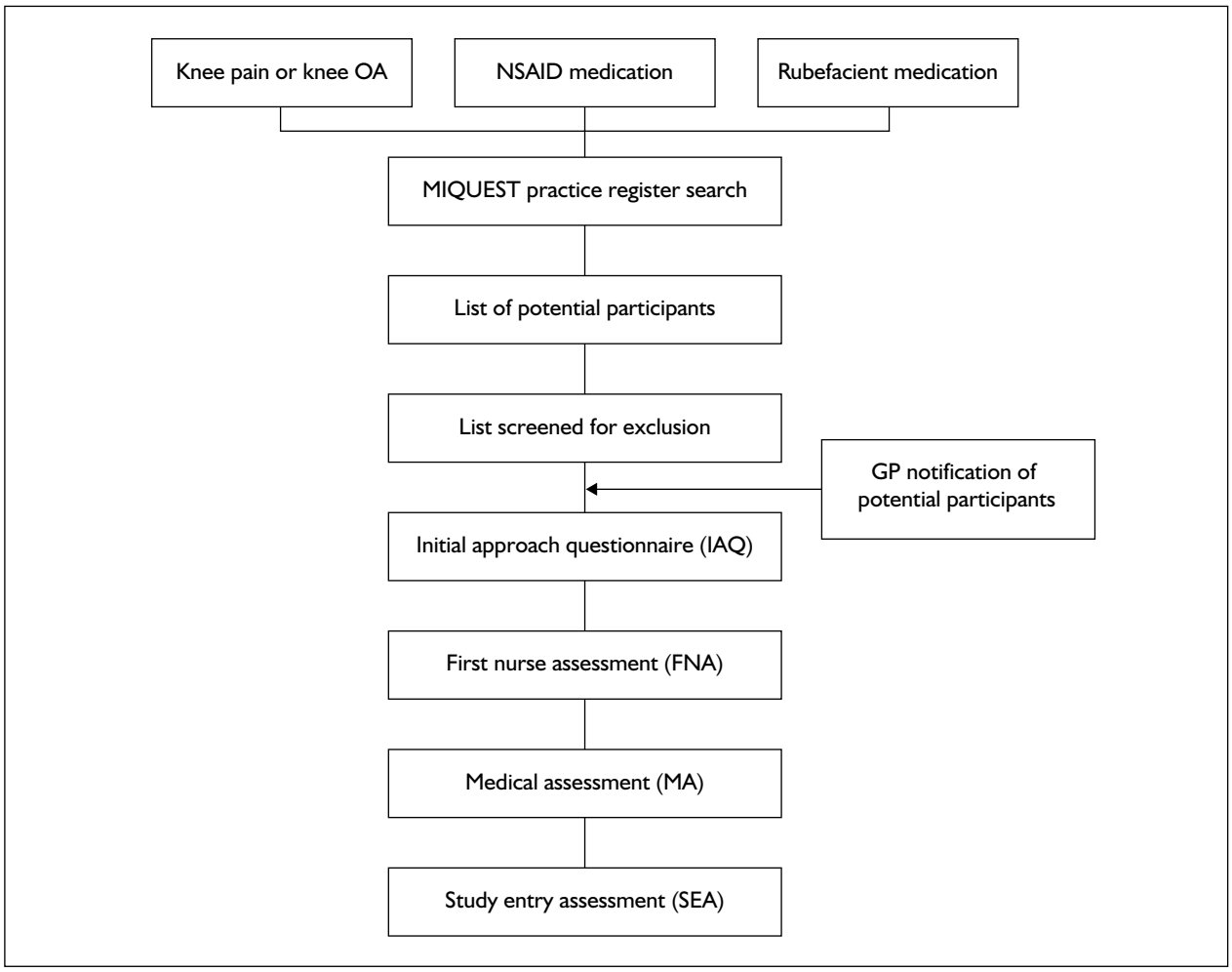


FIGURE 5 *Participant identification*

TABLE 9 *Participant inclusion criteria*

Inclusion criterion	Considerations/definitions	Source of information
Age ⩾50 years	Initially we limited recruitment to those aged 65 years or over. However, early in the recruitment phase it became clear that we were not going to reach our recruitment target. In part this was because older patients appeared more interested in joining the PPS than the RCT. Also, since older people are more likely to have multiple pathologies, many were not eligible for the study as they did not meet safety criteria. With the agreement of the Trial Steering Committee and the MREC, we widened the age criterion. We did not set an upper age limit	Initial sampling
Knee pain	To have troublesome pain in or around the knee on most days for at least 1 month and have experienced knee pain for more than 3 months out of the preceding year[4,101]	IAQ, FNA and SEA
Recently consulted	Consultation with, or treatment prescribed by, the GP for knee pain in the preceding 3 years. Initially this had been set as consultation or treatment within the preceding year. However, early in the recruitment phase it became clear that this was excluding potential participants with ongoing problems who had not had recent contact with their GP about knee pain. With the agreement of the Trial Steering Committee we broadened this entry criterion to 3 years	FNA and MR
Consent	Participant gave informed consent	
Agreement to use chosen/allocated treatment from participant and GP	Participant agreement to use chosen or allocated treatment Participant's GP's agreement to prescribe oral/topical ibuprofen. The GP needed to agree that s/he would be prepared to prescribe either topical or oral medication for the participant if the trial was not taking place. This criterion applied to all participants, including those in the PPS who chose a topical preparation	IAQ and MA
Literate	Able to complete postal questionnaires	IAQ

FNA, first nurse assessment; IAQ, initial approach questionnaire; MA, medical assessment; MR, medical record; SEA, study entry assessment.

PPS were informed that they would have a choice as to which study to join if they decided to take part. We used an identical screening process for both studies; in particular, we applied the same safety criteria to those who expressed a wish to join the PPS and the RCT. At the time of randomisation, participants were formally asked if they wished to join the RCT or PPS, and their treatment preference if they wished to join the PPS. In practices recruiting to the RCT only, participants were not informed of this last preference study option.

Initial approach questionnaire

To control individual practices' workload, the number of potential participants included in the screening process was initially capped at the first 1000 individuals identified from the computer search; output was presented in a random order. Later in the study, some practices had capacity to approach those initially excluded by this capping process. The practice research nurse sent potential participants an invitation to participate, a trial information sheet and the IAQ to screen for eligibility. The research nurse invited those responders with troublesome knee pain in the previous year who were interested in participating and had not had a knee replacement for a first assessment.

Baseline data information is given in *Tables 11–13*.

First nurse assessment

The practice-based research nurse contacted interested patients who, from the IAQ, appeared eligible to attend for the FNA. Initially potential participants were given an appointment to visit the nurse for this assessment. However, early in recruitment it became clear that considerable numbers of potential participants were ineligible, either because they did not meet the knee pain entry criteria or our safety criteria. In the IAQ we asked a general screening question for the presence of knee pain:

TABLE 10 *Exclusion criteria*

Exclusion criterion	Consideration/definitions	Source of information
Peptic ulceration	Past or current	SEA and MR
Moderate/severe indigestion	Defined as potential participants stating that they had had indigestion in the past 3 months on most days (half or more of the days) at either the FNA or the SEA	SEA and MR
Previous adverse reaction to NSAIDS	Defined as a positive response to the question 'Has your doctor ever told you to stop an anti-inflammatory painkiller because of severe side-effects?' or the potential participant's GP reporting a previous serious adverse reaction to an NSAID	FNA and SEA
Raised blood pressure	Defined as blood pressure ⩾155/95	FNA and SEA
Uncontrolled heart failure	We did not exclude potential participants who were being treated for heart failure. However, if a potential participant's GP considered that s/he had uncontrolled heart failure, s/he was excluded	SEA and MA
Serum creatinine >140 mmol/l	NSAIDs contraindicated if abnormal renal function	FNA
Abnormal liver function	Abnormal liver enzymes sufficient to contraindicate use of NSAIDs. Since liver enzymes reference ranges vary between different laboratories, this decision is at the discretion of the potential participant's GP	FNA and MA
Psychological or psychiatric disorders	Including dementia	MA and MR
Troublesomeness	Not at all troublesome knee pain in the last year (IAQ) or last month (FNA and SEA)	IAQ, FNA, SEA
Knee replacement	One or more knee replacements or awaiting knee surgery	MA and MR
An inflammatory arthropathy	Response to NSAIDs may be different in patients whose knee pain is due to an inflammatory arthritis	MA and MR
Serious injury	Serious injury in the six months prior to study entry	MA and MR
Anticoagulants or oral steroids	Use of NSAIDs contraindicated	MA and MR
Anaemia	Defined as Hb <12.4 g/l for men or <11.8 g/l for women	MA and MR
Malignancy	Excluded if had disseminated malignancy	MA and MR
GP exclusion	Request by the potential participant's GP not to include him/her for any other reason	MA and MR

Please think back over the last 12 months. Please put a tick in one box to show if you have pain or have had pain in:

Both knees
In the right knee
In the left knee
In neither knee.

At the FNA we used more specific questions ascertaining eligibility:

1. *Do you have knee pain today?*
2. *Thinking about the last month, have you had knee pain in either knee for most days?*
3. *Thinking back about the last year, have you had knee pain in either knee for most days?*
4. *Thinking back about the last 3 years, have you seen anyone in the practice about your knee pain?*
5. *Thinking back about the last 3 years, have you had any prescriptions from the practice for painkillers, tablets or ointments for your knee pain?*

TABLE 11 *Baseline personal information*

Data type	Measurement	How collected
Demographic data	Age	IAQ
	Sex	FNA
	Ethnic group (based on 2001 census categories)	IAQ
	Age leaving school	IAQ
	Work status	SEA
	Current or previous occupation	SEA
	Occupation of spouse	SEA
	Gross household income	SEA
	Academic and other qualifications	SEA
Current health care	Use of services in previous 5 years	IAQ
	Planned referral for additional treatment	FNA and SEA
	Use of oral NSAIDs in past year	SEA
	Use of topical NSAIDs in past year	SEA
	Use of other pain killers for knee pain in past year	SEA
	Use of any painkillers in previous week	SEA
Expectations, satisfaction and beliefs for treatments	How helpful do they think topical or oral ibuprofen will be?	SEA
	Satisfaction current health state	SEA
	Expectation for pain over coming year	SEA
Health status	Health utility	SEA – EQ-5D
	Health-related quality of life	SEA – SF-36
	Overall pain	SEA – chronic pain grade
	Troublesome pain by region	SEA – troublesomeness grid

EQ-5D, EuroQoL instrument; SF-36, Short Form 36.

TABLE 12 *Baseline clinical information*

Data type	Measurement	How collected
Laboratory investigations	Haemoglobin Creatinine Ferritin Liver function	SEA – practice's usual NHS laboratory. Blood taken at FNA
Physical measurements	Height Weight	SEA – practice's usual equipment
	Peak expiratory flow Forced expiratory volume	SEA – Clements Clarke one flow tester ATS 94 spirometer (best of three readings)
	Blood pressure	SEA – average of three readings using a Compact Dinamap (Johnson and Johnson)

(Eligibility was confirmed with positive answers to both questions two and three and either four or five.)

The more stringent questioning at the FNA at least partly explains why not all of those assessed met our entry criteria. Subsequently, the nurses contacted potential participants by telephone prior to the FNA visit to ask the initial screening questions. If the potential participant became ineligible at any point, the remaining questions were not asked. If the potential participant remained eligible, s/he was asked to attend the practice for the remainder of the assessment. At this visit, a full study explanation was given and interim consent was sought for access to the patient's medical records. Eligibility was assessed, blood pressure measured and blood taken for full blood count, renal function, liver enzymes and serum ferritin. All blood samples were analysed using the usual NHS laboratory used by participating practices.

TABLE 13 *Baseline medical history*

Data type	Measurement	How collected
Medical history	Knee pain troublesomeness in the worst affected knee in last month	SEA
	Knee pain, related pain and disability in past 48 hours	SEA
	Onward referral for further care planned	SEA
	Consultation for knee pain/OA in previous 3 years	SEA
	Recent use of oral or topical NSAIDs and other painkillers	SEA
	On drug treatment for hypertension	SEA and MR
	Ever had a diagnosis of asthma	SEA and MR
	Ever had a diagnosis of chronic obstructive airways disease	SEA and MR
	Prescribed inhalers for chest in last year	SEA and MR
	Prescribed medication for dyspepsia in the last year	SEA and MR
	Prescribed medication for heart failure in the last year	SEA and MR
	Ever had a diagnosis of heart failure clinically	SEA and MR
	Ever had a diagnosis of heart failure confirmed on echocardiogram	SEA and MR
	Days of indigestion in previous three months	SEA and MR

If the potential participant appeared eligible and was interested in participating, the nurse invited him/her for an MA with one of the GPs and a subsequent SEA with the research nurse. Potential participants were asked, where possible, not to use any topical or oral NSAIDs for 1 week before the study entry assessment.

Medical assessment

Between the FNA and SEA potential participants attended for a brief medical assessment (MA) by a GP to identify the physical components of the ACR clinical criteria for knee OA: crepitus, bony tenderness, bony enlargement and no palpable warmth.[8]

The GP also confirmed, in the light of the laboratory results and with access to medical records (MRs), the participant's potential eligibility for the study, and confirmed that s/he would be willing to prescribe either oral or topical ibuprofen for this potential participant. A patient with contraindications to either oral or topical ibuprofen could not enter the study. The GPs completed the assessments after the FNA, and any patient considered ineligible to continue was not invited for the study entry assessment.

Study entry assessment and baseline questionnaire

At the SEA (timed at least 1 week after the FNA so that the blood test results and the medical assessment would be available), the research nurse confirmed that the potential participant:

- still met the knee pain eligibility criteria
- met the safety criteria for study entry, including mean baseline blood pressure measurements
- understood the study and wished to participate.

Assessment procedures were identical for the RCT and the PPS. After written informed consent had been obtained, the participants were asked to complete the study entry questionnaire to establish baseline health and pain data. The research nurse then collected the remaining baseline data. At the end of the SEA, those consenting to join the RCT were randomised using a telephone randomisation service.

All participants were provided with a starter pack of their chosen/allocated treatment when randomised so that they could begin treatment immediately. After this, patients were either prescribed medication by their GP or they could purchase their own over the counter; they were asked to comply with the route of administration they had chosen or been allocated to. Thus, all the baseline assessments were completed before study entry and participants received their first medication immediately after study entry. In a few cases, participants joining the RCT were assessed outside normal office hours when the telephone randomisation service was not available. For these participants, we used a fax randomisation service; randomisation and provision of starter pack took place on the next working day.

Blood pressure screening

Potential participants with a systolic blood pressure of 210 mmHg or more or a diastolic blood pressure of 120 mmHg or more on any occasion were excluded completely. To enter the study, potential participants had to have a systolic blood pressure of less than 155 mmHg and a diastolic blood pressure of less than 95 mmH. Potential participants who at the FNA had a blood pressure of $\geq$155/95 and $<$210/120 mmHg attended for up to two extra visits. Revision or starting of

antihypertensive treatment could be carried out prior to these additional visits to the nurse. If a subsequent blood pressure was <155/95 mmHg they were eligible to enter the study. Participants were excluded if the mean of three blood pressure readings at the study entry assessment was ≥155/95 mmHg. This definition was used for raised blood pressure, taken when not using NSAIDs, to avoid the possibility that participants' blood pressure might be iatrogenically raised into the range requiring treatment when they started ibuprofen. This was a concern because NSAIDs may increase mean blood pressure by around 5 mmHg.[102]

Randomisation process

A remote telephone randomisation service was used, based at the Medical Research Council Clinical Trials Unit, which was housed in a separate building from any of the study team. The practice nurses contacted the randomisation team, who used a computer-based randomisation process to register patients joining the study and to allocate RCT participants to treatment groups. The study team was blind to the participants' chosen/allocated treatment until all of the data required for the primary analyses had been collected. Randomisation was stratified by practice and severity of pain.

Study-specific training and quality control

Before the start of the study, each practice-based research nurse had a full day of training in the study procedures. This included background to the study, informed consent procedures, standardisation of measurements, data collection and management using customised software. An experienced GPRF regional nurse visited all research nurses at least once during the study period to ensure that the protocol was adhered to using GPRF standard operating procedures (Appendix 2). Those regional nurses who were themselves participating in the study were visited by a senior nurse from the GPRF coordinating centre (LL). Each practice nurse received a standard operating procedure manual with a helpline number for queries and problems.

Participant follow-up

Participants were followed up at 3, 6, 12 and 24 months after trial allocation, by postal questionnaires, with two reminders. After 12 and 24 months (or at the end of the study), participants visited the practice to have their blood pressure and respiratory function measured, and blood taken for full blood count, serum ferritin, creatinine and liver enzymes. The practice nurse could visit participants who were unable to attend surgery for annual follow-up at home. The medical records (MRs) were examined 12 months after randomisation to identify unplanned hospital admissions, and after 24 months (or at the end of the study) to collect health service activity data and confirm reported changes in medication and adverse effects. Participants were flagged at the NHS central registry to ensure that all deaths and changes of GP were identified. We were unable to complete 24-month follow-up on all participants. For this reason, those who had completed at least 16–24 months of follow-up at the end of the data collection phase had an end-of-study assessment at this time. Participants due to have 12–16 months of follow-up had an end of study assessment at 12 months. The follow-up flow chart is shown in *Figure 6*.

The intervention

The two interventions being compared were GP's recommendation (either a prescription or advice to get an over-the-counter preparation) to use preferentially either topical or oral ibuprofen. For those whose chosen/allocated treatment was oral ibuprofen, practices were asked to use no more than 1.2 g/day. Treatments for knee pain other than NSAIDs could be used as each patient's doctor thought appropriate. If a change of medication was required, GPs and participants were encouraged to use an alternative NSAID with the same route of administration. Within each practice, the research nurse was responsible for ensuring that the GPs were familiar with the study interventions. Details of the study were filed in each participant's medical record and the record flagged to indicate that they were TOIB study participants, with a reminder to the prescriber about whether to use oral or topical NSAIDs. The exact nature of the flagging and the reminder varied according to the record systems used in each practice. Additionally, we provided each participant with a credit card-sized carrying card with brief details of the study and their treatment allocation to use in case they required treatment elsewhere.

Adherence

Adherence with chosen/allocated treatment was assessed using:

1. A summary of GP prescriptions issued for the trial participants, converted into defined daily doses for topical/oral ibuprofen and other topical/oral NSAIDs.
2. Participant self-report of the number of times they had used pain killing tablets or topical preparations in the month previous to each of

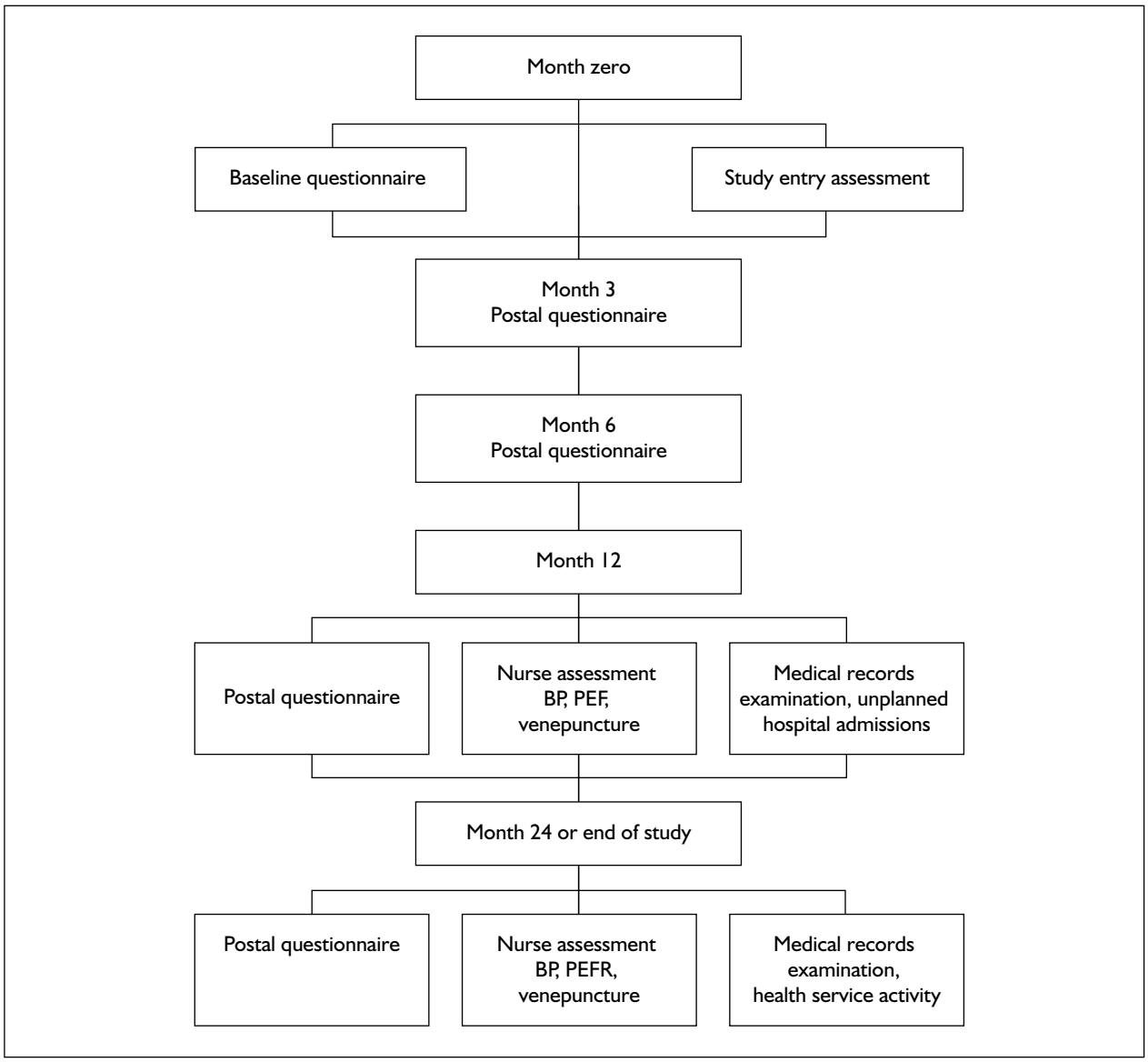


FIGURE 6 *Follow-up flow chart*

the questionnaires, plus information from the same questionnaires on whether they had changed treatment during follow-up.

3. Monitoring of the use of other prescribed analgesic medications, also converted into defined daily doses, reported separately as paracetamol/paracetamol–mild opioid combinations, mild opioids and strong opioids, then pooled as a measure of 'rescue medication' needed when study treatments were ineffective.
4. Prescriptions for drugs used to treat NSAID-related adverse effects, gastrointestinal, cardiovascular and respiratory.

Defined daily doses of NSAIDs

For oral preparations of NSAIDs, we used defined daily dose (DDD) values provided by the WHO Collaborating Centre for Drugs Statistics Methodology (http://www.whocc.no/atcddd/, accessed 9 December 2006). The DDD of oral ibuprofen is 1.2 g. The DDD for topical preparations was more difficult to determine. With the exception of topical diclofenac solution, we were unable to identify any existing values for DDDs of topical NSAIDs to treat one knee, either from the published literature or from correspondence with manufacturers. Some *ex vivo* studies of the penetration of ibuprofen into the knee joint and peri-articular structures have used a defined daily dose of topical ibuprofen. However, the amount used in these studies was substantially larger than the dose one might expect to use in routine practice: 7.5 g of 5% ibuprofen gel three times daily, which provides 1.125 mg of ibuprofen per day from 22.5 g of

gel.[57] This dosage regimen would mean that a 100-g tube of gel would last just 4.4 days, which would be unrealistic for routine use.

We used two approaches to define a daily dose of topical NSAID for one knee:

1. *Loading dose for topical preparations*
   Typical loading doses for topical preparations are 2 mg vehicle/cm^2 of skin (Miller M, Dermal Laboratories: personal communication, 2004).[103,104] To obtain a rough estimate of a single application for topical preparations, we needed an estimate of the surface area of the skin over the knee into which a topical preparation is rubbed and absorbed, and the recommended frequency of administration. We were unable to identify any previous estimates for the surface area of the skin over the knee or those parts of the knee to which patients typically apply topical preparations. A further complication was that the surface area of the knee varies according to its degree of flexion. Hence any estimate of a defined daily dose for treating one painful knee is very crude. We estimated the knee surface by considering the knee as a cylinder. We used the knees of 15 members of the public over 35 years of age for our calculations. We measured the circumference of the extended knee at the level of the superior aspect of the lateral and medial epicondyles of the femur, the joint line and the tibial tuberosity. The mean of these values was taken to be the circumference. We measured the vertical height of the extended knee from the superior border of the patella to the insertion of the patella tendon at the tibial tuberosity. We multiplied height by circumference and divided the result by two because ointments are generally applied to the anterior aspect of the knee only. The average surface area of the anterior of the knees measured was 274 cm^2. This was multiplied by 2 mg to provide an estimate of a single application (0.55 g). The surface area of the skin over the knees of our sample may not be typical of the knees of study participants. However, the number of other assumptions we have made means that we can tolerate this level of potential inaccuracy.
2. *Fingertip units*
   The fingertip unit of creams and ointments can be used to tell patients how much dermatological preparation to use. This is approximately 2.5 cm of vehicle squeezed from a tube on to the distal phalanx of the index finger. This weighs approximately 0.5 g and covers approximately 318 cm^2.[105] This is the amount needed to rub into an area similar to the anterior aspect of the knee. This approach suggests that a single application of ointment is 0.5 g.

Since both approaches came up with a similar value, we have defined a single application as 0.5 g for our further analyses. Manufacturers' recommended frequency of administration for topical NSAIDs varies. Typically for topical ibuprofen they recommend three or four times per day. We have standardised on a three times daily regimen for all preparations. This makes a defined daily application of a topical NSAID cream, gel or ointment for one knee 1.5 g, which for ibuprofen 5% equates to 75 mg of ibuprofen per day (a 10% preparation concentration would equate to 150 mg). These doses of ibuprofen are substantially less than the 1125 mg/day used in *ex vivo* penetration studies; 7% of that used by Dominkus and colleagues.[57] Few prescriptions for topical NSAIDs are for more than 200 g, and to rub in the 7.5 g of vehicle used by Dominkus and colleagues would require a skin area of 600 cm^2. Hence, we are confident that we have a realistic defined daily dose of medication for one knee.

For this study, we defined a daily dose as an application of 1.5 g of ibuprofen or any other topical NSAID ointment/gel/cream or rubefacient preparation. We recognise that the amount of active ingredient absorbed will vary, depending on the concentration of the preparation. However, the actual amount of vehicle applied is likely to be unaffected by the concentration of any active ingredients.

The nature of the study meant that we would not expect patients to be taking the prescribed treatment all the time, as sometimes they may not have much pain. At other times they might be using more than our defined daily dose, particularly if they were treating multiple painful areas with a topical preparation. We assessed poor adherence by the amount of non-allocated treatment that was prescribed. Primarily we considered participants to be adhering to their chosen/allocated treatment if they were prescribed more DDDs of NSAIDs by their chosen/allocated route than by the alternative route. Patients not being prescribed NSAIDs who were being prescribed other painkillers were also deemed not to be adhering to their chosen/allocated treatment. Additionally, we used patient self-report of the number of days in the last month they had used topical or oral NSAIDs.

Blinding and protection against bias

The study was not blinded at practice or patient level. The main study team were blind to participants' chosen/allocated treatment throughout. The trial statistician, who was not involved in data collection, had information on chosen/allocated treatment for the data monitoring and ethics committee, and for checking of self-reported adherence. Other checks were made without reference to the treatment group. The analysis plan was agreed before treatment allocation data were received. There might be bias caused by either the practice nurse's or the patient's knowledge of treatment in their reporting of adverse effects. Participants from one pilot practice took part in the initial qualitative study; data from this practice were not used in the final analysis as being interviewed might have affected participants' decisions about, and response to, treatment. Participants who took part in the later qualitative studies were included in the final analysis as they were interviewed after they had finished follow-up. The qualitative researchers were separate from the quantitative researchers. The trial statistician provided the qualitative team with participants' treatment allocation status and details of those patients who had experienced minor adverse effects, to inform the purposive sampling.

Outcome measures

Our primary outcome measure was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire. We also collected data on possible adverse effects, changes in treatment and range of other health outcome measures.

Primary outcome measures

WOMAC

The WOMAC questionnaire measures knee pain and disability in the preceding 48 hours.[106,107] It produces measures of pain, stiffness and physical function and a global patient assessment. This is a widely used outcome measure for studies of knee OA, which produces two of the three patient-centred measures recommended in the OMERACT consensus statement on the reporting of Phase III trials in OA (pain and physical function).[108]

Major possible adverse effects

A major possible adverse effect was defined as an unplanned hospital admission (including major gastrointestinal complications) or death during the follow-up period. Deaths and their certified causes were identified from practice records and from flagging participants at the NHS central registry. To identify unplanned hospital admissions during the study, we relied on participant completed questionnaires and examination of the participants' MRs by the practice-based research nurse. Additionally, the practice-based research nurses were asked to send an event notification form if, during the follow-up period, any participant had an unplanned hospital admission, had upper gastrointestinal bleeding or died. Prior to each data monitoring and ethics committee meeting, this information was specifically requested. At the end of the study, practices provided anonymised photocopies of all hospital discharge letters for study participants. Two members of the study team (PC and MU, blind to study allocation) independently coded these as planned or unplanned admissions. In addition, they recorded the duration and cause of each admission to hospital for the health economic analysis.

Minor possible adverse effects

The TOIB trial was not powered to show a difference in individual major adverse effects. For example, to show a difference in serious gastrointestinal complications, a much larger study, similar in size to large industry-sponsored trials, would be needed.[45,109,110] Instead, we measured the comparative rates of minor adverse effects.

All non-major adverse effects were described as minor. We recognise that for individual participants these may be important life events or may be a marker for more serious health problems. However, they are quantitatively different to deaths or problems requiring an unplanned hospital admission.

Minor adverse effects were defined using the results from a modified Delphi consultation of GPs with an interest in musculoskeletal problems (Chapter 3). A minor adverse effect was defined as a change in one or more selected parameters that the majority of our Delphi panel considered serious enough to entail advising a change of treatment.

Our data were used to measure the incidence of the minor adverse effects defined in our Delphi study in three categories: gastrointestinal, renovascular and respiratory and overall (*Table 14*). The mean difference or difference in proportions as appropriate for blood pressure, peak flow, Hb, ferritin, creatinine and liver enzymes was also reported. Finally, there was participant self-report of changing treatment due to adverse effects.

TABLE 14 *Minor adverse effects criteria*

Delphi-defined adverse effects		
Gastrointestinal	**Renovascular**	**Respiratory**
• Hb <11.3 g/dl (male) • Hb <10.6 g/dl (female) • Fall in Hb ⩾1.6 g/dl • Ferritin below lower limit of normal • Indigestion more than occasionally • Increase in indigestion by ⩾one category[a]	• Creatinine ⩾152 mmol/l • Increase in creatinine ⩾20 mmol/l • Increase in systolic BP increased by ⩾20 mmHg • Increase in diastolic BP ⩾10 mmHg • New diagnosis of heart failure	• New diagnosis of asthma, COPD • New treatment for asthma or COPD • ⩾15% fall in peak flow

[a] No days; a few days (occasionally); more than occasionally, but fewer than half the days; most days (half or more of the days); every day.

Secondary outcome measures

1. The EuroQol EQ-5D, a well-established measure of health utility,[111,112] which assesses five areas: mobility; self-care; usual activity; pain/discomfort; and anxiety/depression.
2. The postal version of the Chronic Pain Grade, which measures overall pain and pain-related disability over the preceding 6 months.[113,114]
3. The Short Form 36 (SF-36) version 2, a well-established measure of health-related quality of life reported as a physical component score and a mental component score.[52,115,116]
4. Troublesomeness grid, a measure of the troublesomeness of pain in different body regions over the previous month.[117] This allowed the measurement of differences in pain troublesomeness in other body regions where older people with knee pain most commonly have co-existent pain (hip, ankle/foot, back).
5. Satisfaction with health state if the participant had to live the rest of his/her life with the current pain in the worse affected knee using a five-point Likert scale (from very dissatisfied to very satisfied) derived from previous work on back pain.[118]
6. Participants' expectations for the future of pain in their worst-affected knee, measured on a five-point Likert scale (from much worse to much better), with an additional option for an expectation to be pain free derived from previous work on back pain.[119]

In addition to using the WOMAC scores (our primary outcome measure), measures of overall pain and pain in specific body regions were included. Although the focus of this study is on knee pain, it is important to measure any differences in pain more generally, as oral NSAIDs would be more likely than topical NSAIDs to have effects distant to the knee. The satisfaction with health state and troublesomeness of knee pain questions give an indication of participants' global assessment of treatment, a core outcome in the OMERACT consensus recommendations.[108] Radiological imaging, the final OMERACT consensus recommendation for a core outcome measure in long-term studies of OA, was excluded because measuring radiological change was not the focus of this study.

Prescribing data

At the end of the study, practices provided the researcher with details of all prescriptions issued by the practice to participants during the study period. These provided information on all drugs and other items prescribed, their strength and the number of items. For drug groups of particular interest, the number of DDDs of medication in each prescription was estimated. Where available, we used DDD values provided by the WHO Collaborating Centre for Drugs Statistics Methodology (http://www.whocc.no/atcddd/, accessed 9 December 2006). For topical NSAIDs and rubefacient a DDD of 1.5 g/day per knee (see 'Defined daily doses of NSAIDs' on p. 26) was used. We report ibuprofen and other NSAID use separately. DDDs of aspirin were estimated as if it was being used for cardiovascular disease. Nevertheless, aspirin data are presented separately as we cannot be certain in an individual case if it is being prescribed for its anti-platelet actions or as a painkiller. All compound analgesics containing paracetamol, for example co-codamol, have been included in our paracetamol group. Opiate prescriptions have been divided into 'mild' and 'strong' depending on whether the BNF[43] suggests that their use is for mild/moderate or moderate to severe pain. DDDs of paracetamol, mild and strong opioids were pooled to give an estimate of

the overall use of 'rescue analgesia' where NSAIDs have been ineffective or have not been tolerated. An estimate was made of the number of DDDs prescribed in three drug groups that may be used to treat NSAID-related adverse effects: indigestion remedies, respiratory drugs and cardiovascular drugs.

Statistical considerations

Sample sizes

The sample size estimate was based on the primary efficacy measurement at 12 months. Previous work has shown that minimum differences in WOMAC pain and disability scales perceptible to patients are around 10–12 mm on a 100-mm VAS.[120] Typical SDs for the change between baseline and follow-up in knee OA trials are around 22 mm. The primary analysis was the difference between groups in the change from baseline in WOMAC means score with 95% CIs. To show a difference of 10 mm with 90% power and 5% significance we needed analysable data on 103 subjects in each group. Assuming a 75% follow-up rate at 12 months, we needed to recruit 275 participants to the RCT. These numbers would show equivalence to within 10 mm at 80% power. It is usual in equivalence studies to do an on-treatment analysis rather than an intention-to-treat analysis. However, as this study was testing two approaches to managing knee pain, it was agreed with the trial steering committee that an intention-to-treat analysis would be appropriate, although we also did on-treatment analyses of the primary outcome measure and adverse effects. Oral NSAIDs are the standard treatment against which we were comparing topical NSAIDs; it was plausible that either treatment approach could in fact be superior. For this reason, the study was powered for equivalence rather than non-inferiority.

The original expectation was that the RCT and PPS would have fairly similar numbers and that similar numbers of participants in the PPS would choose each of the two treatments. However, early recruitment data indicated a 3:1 preference for topical compared with oral treatment in the PPS, and overall twice as many wanted to join the PPS as the RCT.[121] These facts compromised the original sample size calculations. The RCT was the more important recruitment target so it was agreed with the funders, the trial steering committee and the data monitoring and ethics committee that the last six practices to join the study would recruit participants to the RCT only, the justification being that without the option of the PPS more potential participants would agree to join the RCT. Allowing for the imbalance between the oral and topical groups, we needed to recruit 368 participants to the PPS to achieve 90% power to show a 10-mm difference in WOMAC at the 5% level.

Analyses

Intention-to-treat analyses of primary and secondary outcomes

The RCT and PPS data were analysed separately and on an intention-to treat basis. The primary analyses are all on the 12-month data. For non-categorical data the mean changes between each follow-up period and baseline are presented for each group, along with the differences between the changes in the topical and oral group, separately for the RCT and the PPS. For the topical–oral comparisons, 95% CIs are presented. For the WOMAC and SF-36 components, the figures were calculated using linear regression to adjust for baseline values and the effect of topical versus oral. For other outcomes, *t*-tests were used. Categorical variables are sometimes presented as a whole, but more often presented after being reclassified into binary variables. Differences in proportions and rates between topical and oral groups are given along with 95% CIs as calculated in STATA 9. For categorical variables, if an expected value was below five we used Fisher's exact *p*-values for differences in proportion, rather than CIs for differences in proportions.

Rates of adverse effects are only accurate for emergency hospital admissions as we have the dates for all of these. The date that adverse effects were reported was used in the analyses of rates, and a few with no information such as new diagnoses were considered to have occurred halfway between baseline and the relevant follow-up. For binary outcomes with binary baseline information, logistic regression was used to calculate the effect of being in an oral group or a topical group.

Analyses by prescribed treatment

The effect of being adherent to treatment or not, or taking no painkillers was compared on WOMAC score at 12 months between oral and topical groups using *t*-tests. Multiple regression was used to investigate the joint effects of adherence, group and their interactions on 12-month WOMAC score. Multiple regression was also used to investigate the effect of several classes of painkillers on WOMAC scores.

Similar logistic regression analyses were carried out to explore the relationship between having

had an adverse effect in the first 12 months and prescriptions issued use in the 3 months prior to the 12-month follow-up. Multiple linear regression was used to explore the relationship between measured blood or clinical outcomes at 12 months and prescriptions issued use in the 3 months prior to the 12-month clinical assessment.

Risk-benefit analysis

The relationship between WOMAC score and adverse effects was investigated using a logistic regression model adjusting for age, sex, group and the interaction between group and global WOMAC score. For the measured outcomes at 12 months, the associations between WOMAC score and outcome for each group were modelled after adjustment for age, sex, higher occupational code and baseline values of the outcome measures, and at the same time checking for independent effects of group. These data were then further modelled to adjust for the baseline WOMAC score.

For these analyses, defined adverse events were used that occurred within the period up to and including the date of the 12-month questionnaire, TOIB blood tests or clinical measures of BP and lung function as appropriate. Where there was a report of an adverse effect from the practice but the planned questionnaire or visit to the practice did not happen, the data were included provided that it occurred within 18 months of study entry. Adverse effects which were not present by, or at, the appropriate 12-month follow-up were not included in the 12-month analyses even if they occurred before 18 months.

Deaths and unplanned hospital admissions were analysed if they occurred within exactly 12, 18 and 24 months of study entry.

The drug prescription data used in this analysis were calculated from the prescriptions in the 91 days prior to the measurements of outcome. Where composite measures were used, such as the Delphi defined adverse effects, the prescription data used were those prior to the 12-month questionnaire.

STATA 9 was used for all the analyses (Stata Statistical Software: Release 9, StataCorpLP, College Station, TX, 2005).

Ethical review

Ethical review for all parts of the study was performed by the Northern and Yorkshire Multicentre Research Ethics Committee (MREC 2/3/1). Local approval was provided by 28 Local Research Ethics Committees. Research governance approval was obtained from the seven Primary Care Trusts or Health Boards where work started after the implementation of the Research Governance Framework for Health and Social Care (http://www.dh.gov.uk/policyandguidance, accessed 9 December 2006). The Department of Health acted as sponsors for the study. All research staff with direct patient contact who had no substantive NHS contract held an honorary contract with the relevant NHS body.

Results

Practice recruitment

We recruited 25 practices plus two pilot practices. One pilot practice was included in the final analysis. Our final 26 practices had a registered population of 233,558. Their mean list size was 8983 (range 2922–16,100). The practice distribution was broadly representative of the UK as a whole except that there were no practices in inner London (*Figure 7*). The mean multiple deprivation index for the location of the 20 English practices was 21.15 (range 4.03–60.6). The mean multiple deprivation index for England is 17.02 (http://www.communities.gov.uk, accessed 12 December 2006) indicating that our sample population was selected from areas with slightly

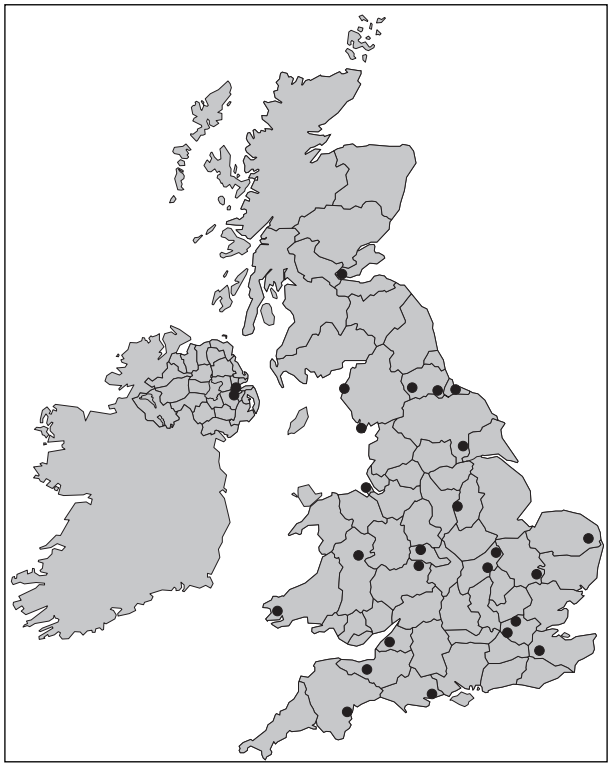


FIGURE 7 *Practice locations*

above average standard of living scores as measured by the multiple deprivation index. The 22 practices in England and Wales came from a mix of localities: industrial (six); resort, sea and retirement (two); cities (two); mixed urban/rural (two); other metropolitan districts (two); outer London (two); remote rural (four); and new towns (two).

Participant recruitment

Participant recruitment took place from April 2003 to May 2005. The follow-up period finished in May 2006. The MIQUEST patient register search identified 26,866 patients; this was 12% of total GP list size (233,558). No approach was made to 3996 (15%) of these who were either excluded by GPs because they were deemed inappropriate to approach for the study or because the practices ran out of time to recruit participants. A total of 22,870 patients were approached.

The attrition rate early in the recruitment process was high (*Figure 8*). Replies were received from 12,704/22,870 (56%) of those approached (*Table 15*). Of these, 3722 (29%) appeared eligible and were interested in the study. For 855 (23%) of these we were unable to arrange an FNA. This was either because it was not possible to arrange an appointment before the end of study recruitment in the practice concerned or because when contacted they were no longer interested in participating. Appointments were made for 2867 FNAs, 2859 of these were carried out. Of those who had an FNA, 913/2859 (32%) failed to meet the knee pain entry criteria (*Table 16*). This was due, at least in part, to the fact that we used more stringent criteria for knee pain at the FNA than in the initial approach questionnaire. A further 609, 36% of those eligible at this stage, failed the safety criteria derived from the clinical history, and 86, 8% of those eligible at this later stage, failed the blood pressure safety criteria. The mean age of those excluded on safety grounds at the FNA was 67 years, which is 3 years older than the mean age (64 years) of those who joined the study. Of those eligible and interested at the end of the FNA, 585/745 (79%) eventually joined the study. About 3% of those initially approached eventually participated in the study (585/22,870). Of these, 282 joined the RCT and 303 the PPS. In the PPS, nearly three times as many participants chose the topical route in preference to the oral route (224 versus 79).

At each stage, a few patients were assessed who should previously have been excluded. Eleven participants were entered into the study in error: one with dyspepsia (PPS, topical); two who failed the consultation criteria (one RCT and one PPS, both topical); one with a knee replacement (PPS, topical); and seven with a mean recorded blood pressure at the SEA that was slightly higher than allowed or missing (two RCT, oral, three PPS, oral, and two PPS, topical). We have not used the data from the SEA from these seven participants in our analyses. The participant with a knee replacement was subsequently excluded from our analyses, but we have included the other participants.

Recruitment data regarding MA and SEA are given in *Tables 17* and *18*, respectively.

TABLE 15 *Participant recruitment, initial approach questionnaire*

Reason for loss	Number of losses[a] (*N* = 22,870)	Still eligible after this stage	Proportion lost at each stage (%)
1. No reply	8,974	13,896	39
2. Blank questionnaire returned	1,192	12,704	9
3. Failed questionnaire criteria			
(a) Knee pain criteria not met	4,765	7,939	38
(b) Knee pain not troublesome	222	7,717	3
(c) Knee replacement criteria not met	710	7,007	9
Total failed knee criteria	*5,697*	*7,007*	*45*
4. Not interested in taking part	3,285	3,722	47
5. No appointment for FNA	855	2,867	23
6. Did not attend FNA	8	2,859	< 1
Total not assessed	*20,011*		*87*

[a] Recruitment was sequential; once any potential participant was excluded, no further data were collected. Thus, number of losses is number excluded at each stage. One questionnaire was lost but the patient received all the following questionnaires and so is included at this point as eligible.

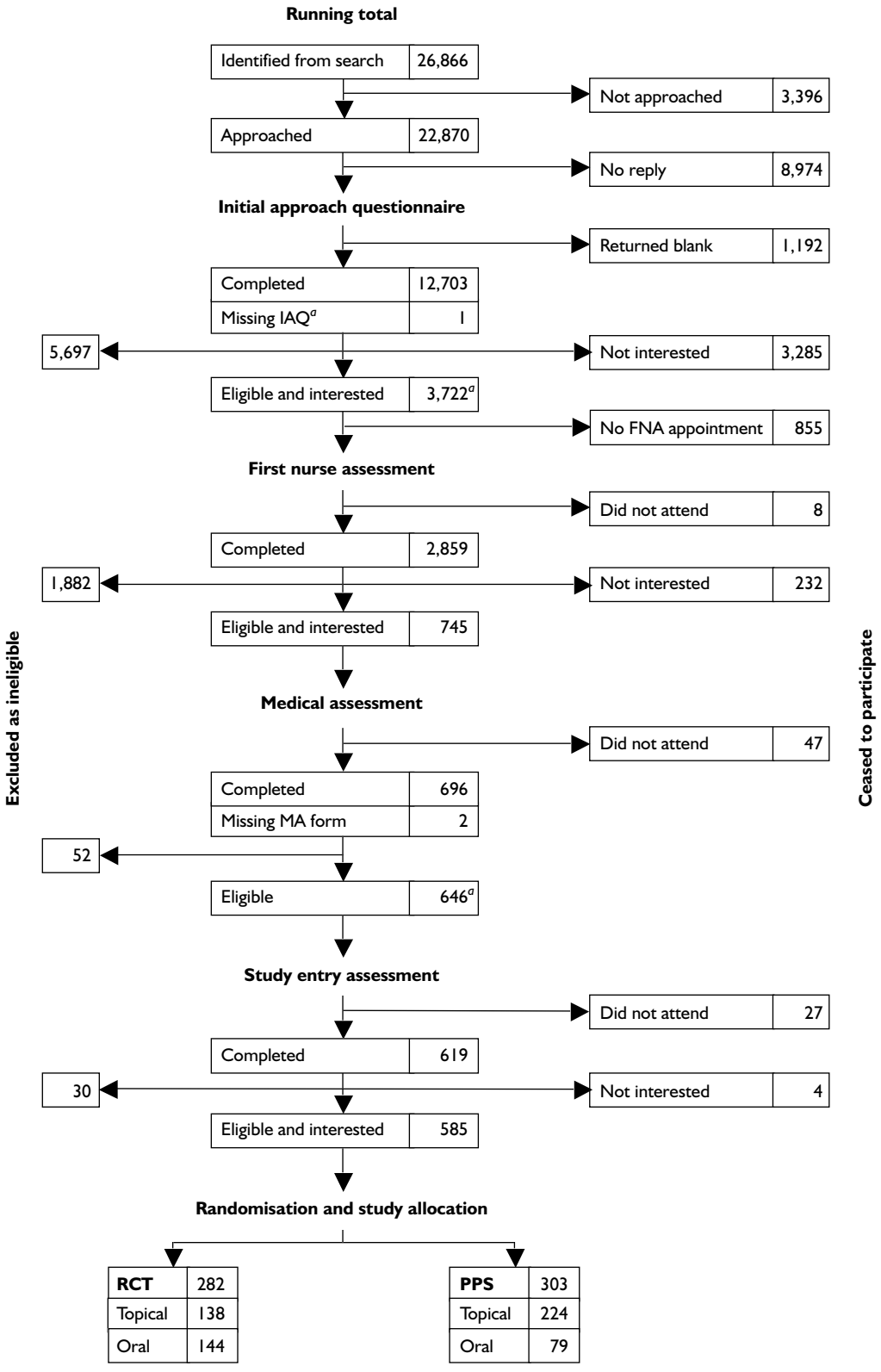


FIGURE 8 *TOIB recruitment flow chart*

TABLE 16 *Participant recruitment, first nurse assessment*

Reason for loss	Number of losses[a] (*N* = 2859)	Still eligible after this stage	Proportion lost at each stage (%)
1. Failed knee pain criteria	913	1946	32
2. Consultation criteria not met	230	1716	12
3. Knee replacement	25	1691	1
4. Safety criteria – history	609	1082	36
5. Troublesomeness criterion not met	7	1075	<1
6. Understanding poor	7	1068	<1
7. Mental state criteria not met	1	1067	<1
8. Not NHS registered	2	1065	<1
9. Systolic >210 or diastolic >120 monthly	6	1059	<1
10. Failed BP subsequently	80	979	8
11. English criteria not met	2	977	<1
Total ineligible	*1882*	*977*	*66*
12. Not interested in taking part	232	745	25
13. Did not attend medical assessment	47	698	5

[a] Two medical assessment forms were lost but the patients did attend study entry assessment and so are included at this point as eligible.

TABLE 17 *Participant recruitment, medical assessment*

Reason for loss	Number of losses (*N* = 698)	Still eligible after this stage	Proportion lost at each stage (%)
1. Failed one or more specified safety criteria	30	668	4
2. GP would not consider giving NSAIDs to patient if study not taking place	16	652	2
3. GP not willing to prescribe NSAIDs for this patient within the study	6	646	<1
Total failed medical assessment	*52*	*646*	*7*
4. Did not attend study entry assessment	27	619	4

TABLE 18 *Participant recruitment, study entry assessment*

Reason for loss	Number of losses (*N* = 619)	Still eligible after this stage	Proportion lost at each stage (%)
1. Knee pain criteria not met	10	609	2
2. Consultation criteria not met	5	604	<1
3. Safety criteria – history not met	8	596	1
4. Understanding poor	1	595	<1
5. Safety criteria – blood pressure	4	591	<1
6. Creatinine >140 mmol/l	1	590	<1
7. Hb <12.4 (men) or <11.8 (women)	1	589	<1
Total ineligible	*30*	*589*	*5*
8. Not interested in taking part	4	585	<1

RCT and PPS baseline characteristics

Age

The mean age for all participants joining the study was 64 years (SD 8.5, median 64), range 50–89 years. The PPS participants' mean age was 66 years (SD 8.2) and for the RCT 63 years (SD 8.4), indicating a slightly older population in the PPS (*Table 19*, *Figure 9*). There was a statistically significant difference in age between the pooled RCT groups and topical and oral PPS groups ($p = 0.0008$). Using a test allowing for multiple comparisons (Sidak), the only statistically significant difference in age between groups was between age in the pooled RCT group and the topical PPS group ($p = 0.001$).

Ethnicity

Of those invited for an FNA, 3706/3722 (99.6%) had given their ethnic group in the participant initial approach questionnaire. Sixty-four categorised their ethnic group as non-white (Asian 28, black 19, other 17). Of those finally enrolled in the study, seven (1%) categorised themselves as non-white (Asian three, black one, other three).

Social class

We used the Standard Occupational Classification System 2000 (Office of National Statistics) (http://www.statistics.gov.uk/methods_quality/ns_sec/downloads/SOC2000.doc, accessed 8 December 2006) to classify the participants into 10 social groups. Occupational data on participants and their partners were requested. If a participant's partner had a higher social class than the participant then this higher social class was used in analyses. An analysis using χ^2 for trend by group indicated that there was a statistically significant difference in social class between the

TABLE 19 *Age distributions by different groupings*

Group	Mean age (SD) (years)	Median (years)	Interquartile range (years)	Range (years)
RCT, oral	62.8 (8.3)	60	56–69	51–84
RCT, topical	62.6 (8.5)	60	56–68	51–85
PPS, oral	64.5 (8.7)	64	57–72	50–89
PPS, topical	66.5 (8.0)	66	60–72	51–87

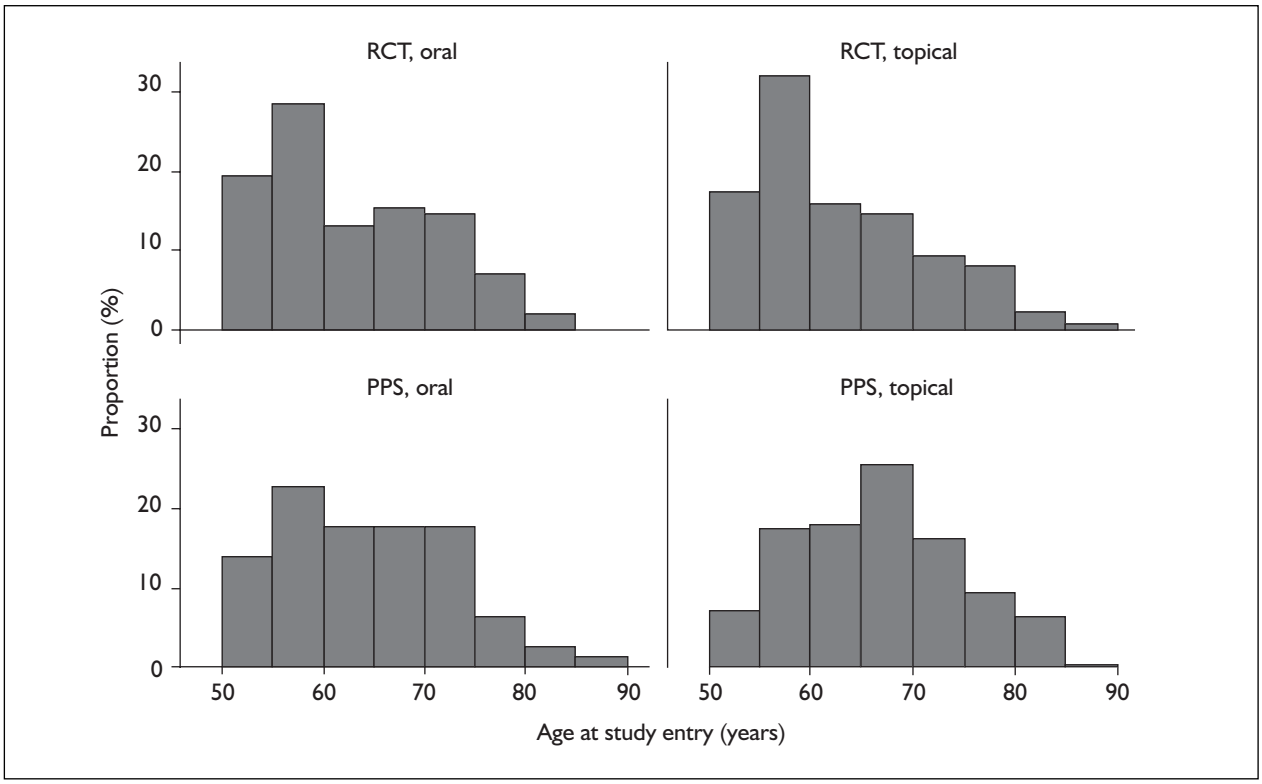


FIGURE 9 *Age distribution of study population*

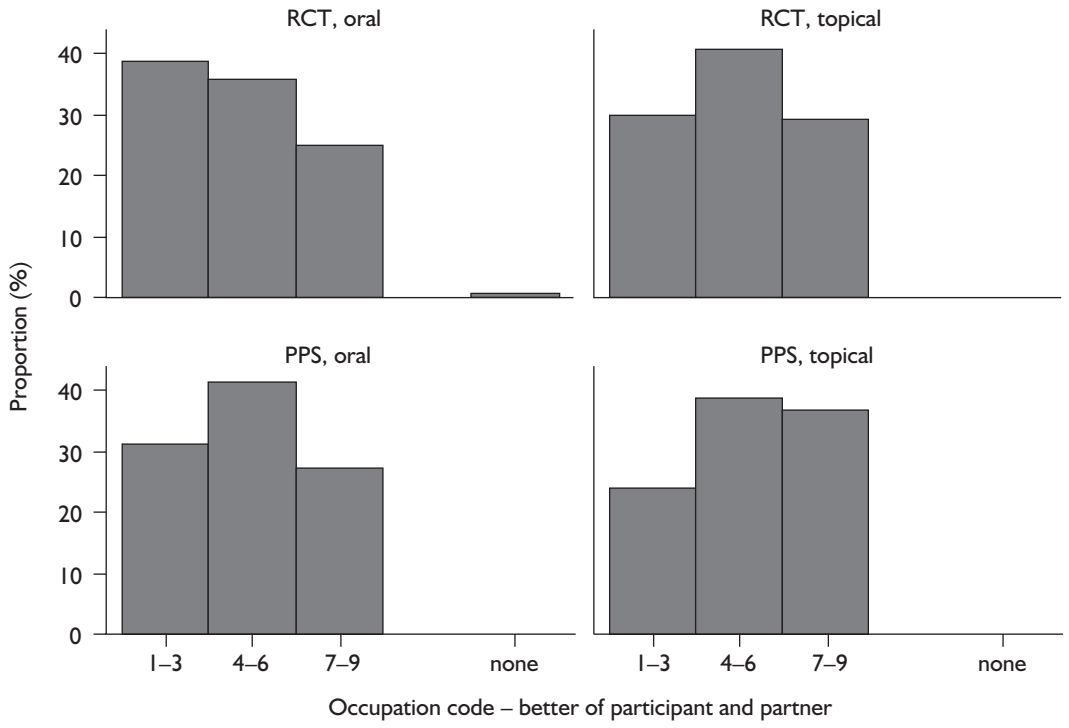
RCT and PPS participants ($p = 0.016$) (*Figure 10*). The RCT participants had a slightly higher social class. The difference between the two PPS arms was not statistically significant ($p = 0.10$). However, as with the effect of age, it would appear that the real difference is between the topical PPS group who were of lower occupational status than the other two groups, which appeared similar. The proportions with occupational codes 1–3 (managers and senior officials, professionals and associate professional and technical), are 29, 31 and 24%, respectively, in the RCT, oral PPS and topical PPS.

Study entry characteristics

Apart from age and social class, participants' main baseline characteristics were broadly similar across all four groups. In particular, there were no differences between the two randomised groups except that in the oral group fewer had used oral NSAIDs and more had used topical NSAIDs in the previous year. Previous NSAID use in the PPS showed that participants were more likely to choose the route of administration they had not used in the previous year. In addition, more of those who chose topical treatment had not been using any NSAIDs in the previous 12 months (*Tables 20–24*).

There were, however, some differences in participants' expectations for treatment. In the RCT, fewer participants in the topical group than the oral groups thought that topical preparations would be very helpful. As predicted, participants in the PPS generally expected their chosen medication to be effective or very effective (*Table 23*). There were also some differences in the PPS in the proportions of the two groups having at least moderately troublesome pains in other body areas. More PPS participants who chose to use oral ibuprofen had at least moderately troublesome pain in one or more additional body area [difference topical – oral 11% (95% CI –1 to –21)] (*Table 20*).

Twenty-six participants (4%) had indigestion more than occasionally, but fewer than half the days. This was one of the criteria identified in our Delphi study as a minor adverse effect. However, when the study was designed we had set our entry



1–3 = managers and senior officials, professionals and associate professional and technical
4–6 = administrative and secretarial, skilled trade, personal services
7–9 = sales and customer service, process, plant and machine operatives and elementary occupations
none = not in paid employment

FIGURE 10 *Occupational classifications distribution*

TABLE 20 *Baseline characteristics*

	Mean (SD)[a]			
	RCT		PPS	
	Oral *n* = 144[b]	Topical *n* = 138[b]	Oral *n* = 79[b]	Topical *n* = 224[b]
Demographic data				
Males	63 (44%)	68 (49%)	31 (39%)	96 (42%)
Mean age at randomisation (median, IQR)	63 (60, 56–69)	63 (60, 56–68)	65 (64, 57–72)	67 (66, 60–72)
Met ACR criteria for OA	140 (98%)	134 (97%)	79 (100%)	217 (97%)
Pain/wellbeing				
WOMAC	*n* = 144	*n* = 135	*n* = 76	*n* = 216
Pain score	39 (21.5)	39 (19.3)	39 (19.3)	41 (20.1)
Stiffness	47 (25.7)	50 (24.6)	50 (22.4)	49 (24.9)
Difficulty	38 (23.1)	37 (18.3)	41 (20.2)	40 (20.4)
Global	39 (22.0)	38 (17.6)	41 (18.7)	41 (19.4)
EQ-5D utility score	*n* = 140	*n* = 138	*n* = 78	*n* = 219
	0.65 (0.22)	0.67 (0.19)	0.63 (0.23)	0.66 (0.19)
Chronic pain grade	*n* = 141	*n* = 136	*n* = 78	*n* = 219
0: no disability – no intensity	0 (0%)	0 (0%)	0 (0%)	0 (0%)
I: low disability – low intensity	55 (38%)	52 (38%)	29 (37%)	86 (38%)
II: low disability – high intensity	36 (25%)	49 (36%)	23 (29%)	66 (29%)
III: high disability – moderately limiting	25 (17%)	21 (15%)	16 (20%)	46 (20%)
IV: high disability – severely limiting	25 (17%)	14 (10%)	10 (13%)	22 (10%)
SF-36	*n* = 138	*n* = 136	*n* = 74	*n* = 209
Physical component score	39.0 (9.7)	39.2 (8.9)	37.7 (7.8)	38.5 (9.4)
Mental component score	52.0 (10.2)	53.7.(9.6)	51.7 (10.4)	52.0 (10.0)
Very/extremely troublesome knee pain	*n* = 144	*n* = 138	*n* = 79	*n* = 224
	45 (31%)	45 (33%)	26 (33%)	6 (29%)
Indigestion in last 3 months	*n* = 144	*n* = 138	*n* = 78	*n* = 224
No days	86 (60%)	78 (57%)	47 (59%)	106 (47%)
A few days (occasionally)	50 (35%)	54 (39%)	28 (35%)	106 (47%)
>occasional, <half the days	8 (6%)	6 (4%)	3 (4%)	11 (5%)
Most days (half/more of the days)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Every day	0 (0%)	0 (0%)	0 (0%)	0 (0%)
NSAID use in the past year	*n* = 141	*n* = 138	*n* = 78	*n* = 223
Used neither	34 (24%)	20 (14%)	8 (10%)	64 (29%)
Used oral only	59 (41%)	81 (59%)	49 (62%)	82 (37%)
Used topical only	9 (6%)	8 (6%)	1 (1%)	40 (18%)
Used both topical and oral	39 (27%)	28 (20%)	21 (27%)	37 (17%)

IQR, interquartile range.
[a] Unless stated otherwise.
[b] Number of participants.

criteria to include this group within the study. Therefore, some participants were included who were already reporting one of our minor adverse effects.

Participant follow-up

Good follow-up rates were achieved (*Figures 11* and *12* and *Table 25*). Response rates were typically in excess of 85% for questionnaire, nurse assessments, blood tests and record examinations up to 12 months. The 24-month follow-up rates were lower but were still all in excess of 70% for the PPS. A lower 24-month follow-up rate was achieved in the RCT. This was because during the latter stages of the study participants were recruited for the RCT only, owing to the

TABLE 21 *Baseline clinical health characteristics*

	RCT		PPS	
	Oral	**Topical**	**Oral**	**Topical**
Blood pressure: average of three readings; mean (SD)				
Last of readings prior to study entry[a]	*n* = 142	*n* = 138	*n* = 76	*n* = 223
Systolic (mmHg)	134 (15)	131 (15)	135 (15)	132 (15)
Diastolic (mmHg)	74 (10)	75 (10)	73 (9)	71 (10)
Lung function: best of three readings; mean (SD)				
At study entry assessment	*n* = 143	*n* = 135	*n* = 78	*n* = 223
PEF (l/minute)	380 (126)	388 (125)	365 (105)	345 (114)
FEV_1 (litres)	2.36 (0.69)	2.42 (0.72)	2.40 (0.71)	2.24 (0.65)
Blood results: mean (SD)				
Hb (g/l)	14.1 (1.1)	14.1 (1.1)	13.9 (1.0)	13.9 (1.3)
Creatinine (mmol/l)	86 (15)	88 (16)	88 (17)	88 (15)
Ferritin (ng/l)	120 (94)	127 (106)	117 (92)	106 (92)
Log_e(ferritin)[b]	4.5 (0.8)	4.5 (0.8)	4.5 (0.8)	4.4 (0.8)

FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow rate.
[a] The seven patients with a higher than eligible mean blood pressure recorded on their SEA forms have not been included in the results.
[b] Log_e(ferritin) was used as ferritin has a highly positively skewed distribution.

TABLE 22 *Expectations and satisfaction with health state at baseline*

	Mean (SD)[a]			
	RCT		PPS	
	Oral	**Topical**	**Oral**	**Topical**
Expectation				
Expectation of pain in worse knee 1 year from baseline (median and IQR)[b]	3 (2–3)	2 (2–3)	2 (2–3)	3 (2–4)
How helpful do you think the tablets will be?	*n* = 144	*n* = 136	*n* = 79	*n* = 222
(% very:% helpful:% not helpful)	30:63:7	28:64:8	44:54:1	11:59:30
How helpful do you think the ointment will be?	*n* = 138	*n* = 135	*n* = 71	*n* = 216
(% very:% helpful:% not helpful)	30:59:10	16:67:17	7:48:45	30:69:1
Satisfaction	*n* = 143	*n* = 136	*n* = 79	*n* = 223
Somewhat or very dissatisfied if one had to spend the rest of one's life with current pain in worst affected knee	97 (68%)	92 (68%)	56 (71%)	152 (68%)

[a] Unless stated otherwise.
[b] Range 1–6: 1, much worse; 3, the same; 5, much better; 6, free from pain.

popularity of the PPS. The available follow-up period for some of these participants was less than 24 months.

Since blood tests for the TOIB trial were carried out at the laboratory normally used by participating practices, data were included in our analyses, where appropriate, from tests done as part of routine patient care. For the 12-month analyses the results were used from the blood test carried out, either as part of the study or as part of routine care, closest to the 12-month follow-up date, so long as they were dated within 6–18 months of joining the study. The mean time to planned blood test if carried out in the first 18 months after joining the study was 1.03 decimal years (SD = 0.09). If the *ad hoc* tests carried out between 6 and 18 months for those without a planned test in this period are included, the mean becomes 1.04 years (SD = 0.10).

TABLE 23 *Other areas of at least moderately troublesome pain (not knee pain) (% at least moderately troublesome)*

Baseline	RCT		PPS	
	Oral *n* = 143[a]	Topical *n* = 135[a]	Oral *n* = 77[a]	Topical *n* = 218[a]
Back	57 (40%)	50 (37%)	42 (55%)	96 (44%)
Hip/thigh	49 (35%)	34 (26%)	40 (53%)	73 (34%)
Shoulder/neck	47 (33%)	48 (36%)	30 (38%)	84 (39%)
Ankle/foot	37 (26%)	32 (24%)	27 (35%)	63 (29%)
Wrist/hand	43 (31%)	32 (24%)	31 (40%)	67 (31%)
Elbow	22 (16%)	22 (16%)	17 (22%)	27 (13%)
At least one moderately troublesome	101 (71%)	97 (71%)	66 (84%)[b]	160 (73%)[b]

[a] *n* = Number who answered the question for the back; there are slight differences for other areas.
[b] *p* = 0.028 (95% CI –1 to –21%), for the comparison between oral and topical groups in the PPS.

TABLE 24 *Completeness of baseline data*

Baseline data	RCT		PPS	
	Oral *n* = 144	Topical *n* = 138	Oral *n* = 79	Topical *n* = 224
Initial approach questionnaire	144 (100%)	138 (100%)	78 (99%)	224 (100%)
First nurse assessment	144 (100%)	138 (100%)	79 (100%)	224 (100%)
Study entry assessment	144 (100%)	138 (100%)	79 (100%)	224 (100%)
Study entry questionnaire	144 (100%)	138 (100%)	79 (100%)	224 (100%)
Liver function test (any)	143 (99%)	133 (96%)	76 (96%)	221 (99%)
Haemoglobin	144 (100%)	137 (99%)	79 (100%)	219 (98%)
Ferritin	137 (95%)	134 (97%)	77 (97%)	216 (96%)
Creatinine	143 (99%)	134 (97%)	78 (99%)	223 (100%)

For the 24-month analyses any data collected in the period between 18 and 24 months after follow-up were used. In addition to the analyses at specified time-points, we did an end-of-study analysis using the last follow-up data collected on each participant. This analysis also included questionnaire data collected between 12 and 18 months from 55 participants who had already completed a 12-month questionnaire but did not complete a subsequent 24-month follow-up questionnaire.

Differences between those with and without follow-up data (non-responders)

Missing follow-up data could be considered in a number of categories:

- failure to complete follow-up questionnaires
- failure of participant to attend for 12-month and end-of-study assessments
- failure to have follow-up blood tests
- failure of the practice research nurse to organise follow-up visits or to complete end-of-study note searches.

Response to the 12-month questionnaire, which provided the primary pain outcome, was used to categorise participants as responders or non-responders. Failure to return the questionnaire is almost completely determined by the patient rather than the practice, whereas for other outcomes non-response was sometimes associated with late booking by the surgery. The number of non-responders in each of the four study groups was small and hence there is little statistical power to assess difference in non-response between or within individual groups. All four groups were therefore pooled for comparison of responders and non-responders. Non-responders were more likely to be men and to have lower educational attainment. Non-responders were statistically significantly likely to have more pain and difficulty, as measured by the baseline WOMAC scores and by the chronic pain grade (*Table 26*).

The only within-group difference to achieve statistical significance was that even more men than women in the topical PPS group compared with the other groups failed to return 12-month follow-up questionnaires ($p = 0.042$ after adjustment for male and topical).

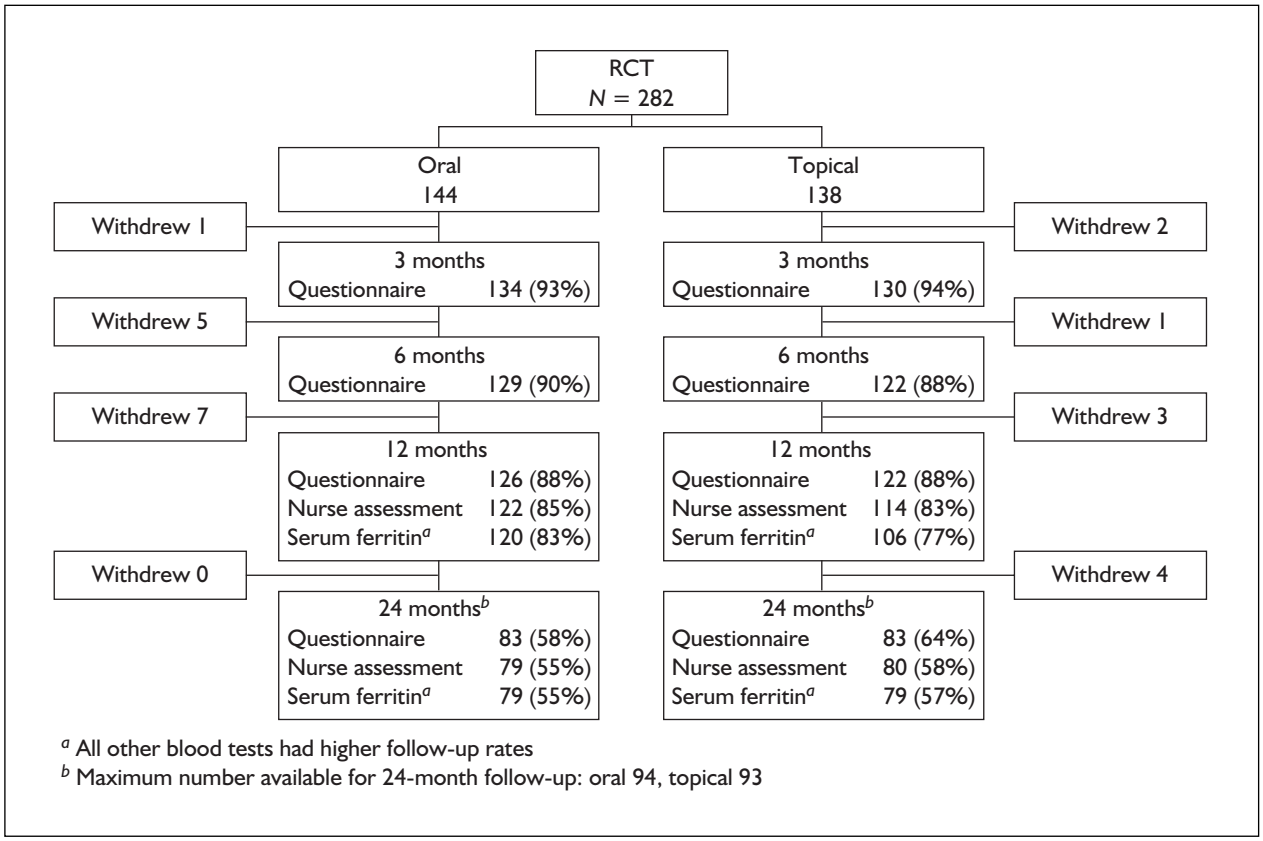


FIGURE 11 *Follow-up flow chart, RCT*

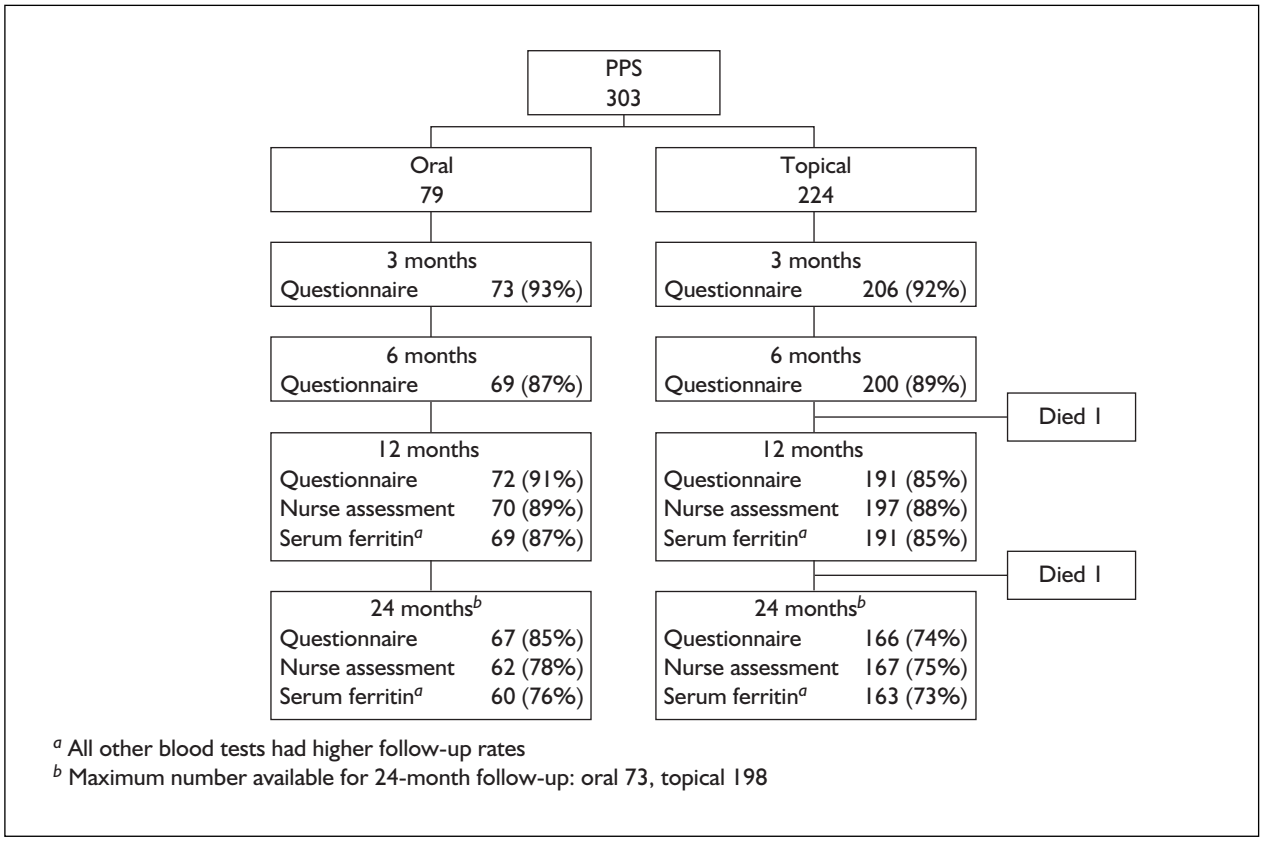


FIGURE 12 *Follow-up flow chart, PPS*

TABLE 25 *Participant follow-up rates*

	RCT		PPS	
	Oral ***n*** **= 144**	**Topical** ***n*** **= 138**	**Oral** ***n*** **= 79**	**Topical** ***n*** **= 224**
3-month patient questionnaire	134 (93%)	130 (94%)	73 (93%)	206 (92%)
6-month patient questionnaire	129 (90%)	122 (88%)	69 (87%)	200 (89%)
12-month information[a]				
Patient questionnaire	126 (88%)	122 (88%)	72 (91%)	191 (85%)
Nurse assessment	122 (85%)	114 (83%)	70 (89%)	197 (88%)
Bloods collected as part of TOIB study between 6 and 18 months				
Liver function test (any)	119 (83%)	105 (76%)	69 (87%)	192 (86%)
Haemoglobin	121 (84%)	105 (76%)	68 (86%)	195 (87%)
Ferritin	119 (83%)	105 (76%)	69 (87%)	190 (85%)
Creatinine	121 (84%)	105 (76%)	69 (87%)	194 (87%)
Bloods collected as part of TOIB study or from practice records between 6 and 18 months				
Liver function test (any)	132 (90%)	113 (82%)	74 (94%)	202 (90%)
Haemoglobin	128 (89%)	113 (82%)	70 (89%)	203 (91%)
Ferritin	120 (83%)	106 (77%)	69 (87%)	191 (85%)
Creatinine	130 (90%)	114 (83%)	73 (92%)	202 (90%)
Any follow-up blood results before 18 months				
Liver function test (any)	134 (93%)	113 (82%)	74 (94%)	206 (92%)
Haemoglobin	130 (90%)	115 (83%)	70 (89%)	205 (92%)
Ferritin	120 (83%)	106 (77%)	69 (87%)	191 (85%)
Creatinine	132 (92%)	115 (83%)	74 (94%)	204 (91%)
24-month information[b]	*n* = 94	*n* = 93	*n* = 73	*n* = 198
Patient questionnaire	83 (58%)	88 (64%)	67 (85%)	166 (74%)
Nurse assessment	79 (55%)	80 (58%)	62 (78%)	167 (75%)
Liver function test (any)	86 (60%)	85 (62%)	61 (77%)	173 (77%)
Haemoglobin	81 (56%)	83 (60%)	62 (78%)	173 (77%)
Ferritin	79 (55%)	79 (57%)	60 (76%)	163 (73%)
Creatinine	87 (60%)	86 (62%)	65 (82%)	173 (77%)
End of study information[c]				
Note search	140 (97%)	136 (99%)	77 (97%)	220 (98%)
Either nurse assessment	128 (89%)	121 (88%)	73 (92%)	206 (92%)
Bloods at 12 or 24 months[a]				
Liver function test (any)	136 (94%)	124 (90%)	76 (96%)	216 (96%)
Haemoglobin	133 (92%)	124 (90%)	73 (92%)	212 (95%)
Ferritin	129 (90%)	116 (84%)	71 (90%)	203 (91%)
Creatinine	136 (94%)	124 (90%)	76 (96%)	213 (95%)
Any questionnaire	140 (97%)	133 (96%)	77 (97%)	214 (96%)
Prescription information	130 (90%)	124 (90%)	76 (96%)	210 (94%)

[a] Data included as 12-month information provided it is completed within 18 months of study entry. The result nearest to 12 months used for the analysis.

[b] Data included as 24-month information provided it is completed more than 18 months after joining the study; that collected nearest to 24 months is used. Denominator for percentages is number of participants included at baseline; *n* = number of people who were in the study long enough to have had a 24-month assessment.

[c] Data from 55 end-of-study questionnaires completed after a 12-month assessment but within 18 months of randomisation have been used for the last value carried forward analysis.

TABLE 26 *Difference between non-responders and responders to the 12-month questionnaire: non-responders minus responders difference (95% CI)*

	RCT		PPS		All
	Oral 18/144[a]	Topical 16/138[a]	Oral 7/79[a]	Topical 33/224[a]	Difference (95% CI)
Difference in					
Mean age at baseline	0.1	4.3	–6.5	1.1	1 (–1 to 3) $p = 0.40$
Mean best occupational code of patient or current partner[b]	1.2	–0.8	0.3	0.5	0.4 (–0.2 to 1.3) $p = 0.18$
Proportion with A-level equivalent or higher qualifications	–11%	–11%	15%	–9%	–8% (–1 to 16%) $p = 0.13$
Proportion male (positive means more men in the non-responders)	1%	1%	4%	25%	12% (–1 to 24%) $p = 0.061$
Proportion with chronic pain grade III or IV	23%	1%	26%	30%	–22% (–34 to –9%) $p = 0.0002$
WOMAC scores					
Pain	11	–1	5	9	7 (2 to 12) $p = 0.008$
Stiffness	13	–8	8	3	4 (–2 to 10) $p = 0.24$
Difficulty	12	–2	9	10	8 (3 to 13) $p = 0.002$
Total	12	–2	8	9	7 (2.5 to 12) $p = 0.003$

[a] Non-responders/total.
[b] Codes 1–9 (excluding 0 and missing data).

Effectiveness and adverse effects outcome data

Primary outcomes

WOMAC scores

There was little difference between the baseline and follow-up WOMAC scores. There were no statistically significant differences in any of the WOMAC outcome scores between topical and oral groups in the RCT or PPS at any time-point (*Tables 27–30* and *Figures 13* and *14*).

After adjustment for baseline scores, no significant differences were found in the WOMAC global scores between topical and oral groups (*Tables 29* and *30*). Only in the RCT 24-month and end-of-study analyses did the WOMAC pain scores show a

TABLE 27 *WOMAC scores, RCT: mean (SD)*

	Baseline	3 months	6 months	12 months	24 months	End of study[a]
Pain						
Oral	30 (22)	37 (21)	37 (21)	36 (23)	34 (21)	36 (21)
Topical	39 (19)	35 (22)	37 (22)	38 (21)	41(22)	41 (22)
Stiffness						
Oral	47 (26)	44 (25)	45 (27)	43 (26)	44 (22)	46 (26)
Topical	50 (25)	45 (26)	45 (25)	46 (24)	47 (26)	46 (26)
Difficulty						
Oral	38 (23)	37 (22)	37 (22)	36 (23)	34 (23)	36 (23)
Topical	37 (18)	35 (22)	38 (22)	39 (23)	39 (23)	39 (24)
Global						
Oral	39 (22)	38 (22)	38 (22)	37 (23)	35 (22)	37 (22)
Topical	38 (18)	36 (21)	38 (21)	40 (22)	40 (22)	40 (22)

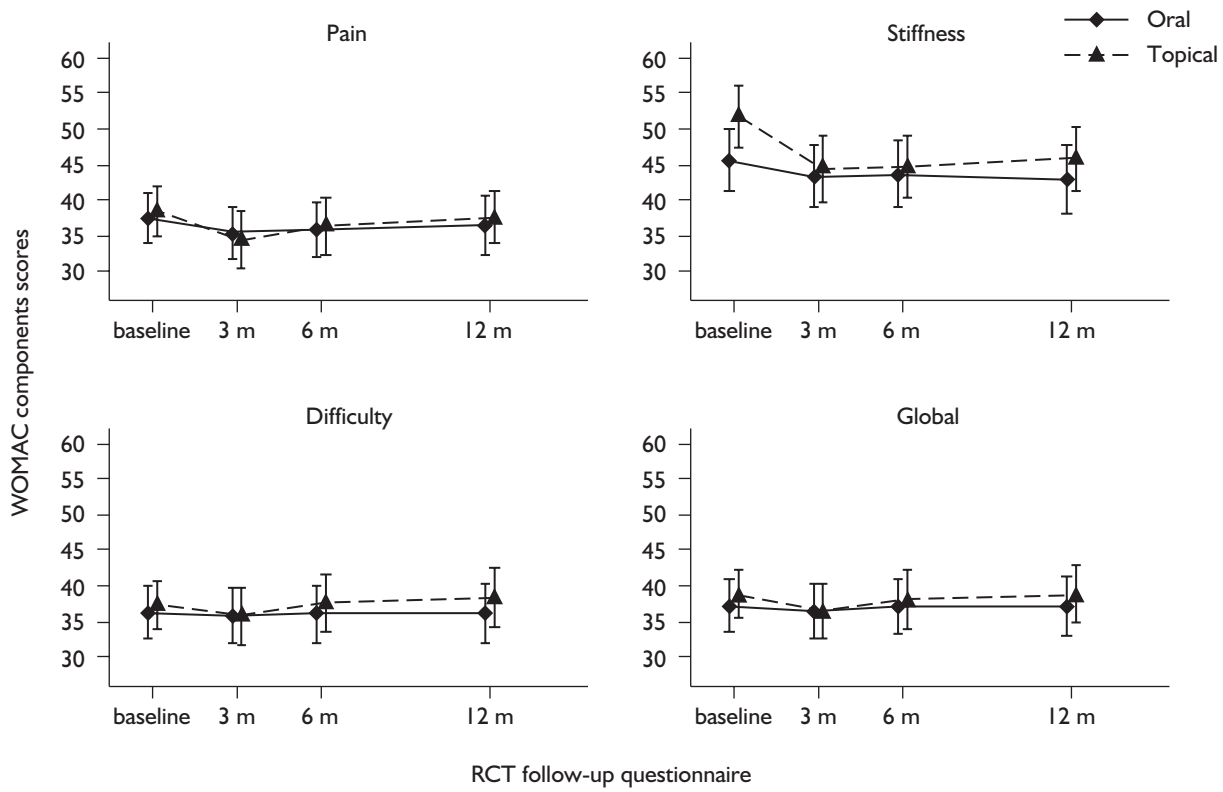
[a] End-of-study value is the last value carried forward or the 24-month follow-up. Score of zero indicates no pain, range 0–100.

TABLE 28 *WOMAC scores, PPS: mean (SD)*

	Baseline	3 months	6 months	12 months	24 months	End of study[a]
Pain						
Oral	39 (19)	39 (20)	39 (22)	40 (21)	38 (21)	39 (23)
Topical	41 (20)	37 (23)	38 (24)	40 (25)	40 (26)	39 (25)
Stiffness						
Oral	50 (22)	45 (25)	47 (25)	49 (24)	48 (24)	49 (24)
Topical	49 (25)	45 (26)	45 (27)	47 (28)	48 (28)	46 (28)
Difficulty						
Oral	41 (20)	38 (23)	37 (21)	39 (23)	40 (22)	41 (23)
Topical	40 (20)	39 (24)	39 (24)	41 (25)	42 (26)	41 (26)
Global						
Oral	41 (19)	39 (22)	38 (21)	40 (21)	40 (22)	41 (22)
Topical	41 (19)	39 (23)	39 (23)	41 (24)	42 (25)	41 (25)

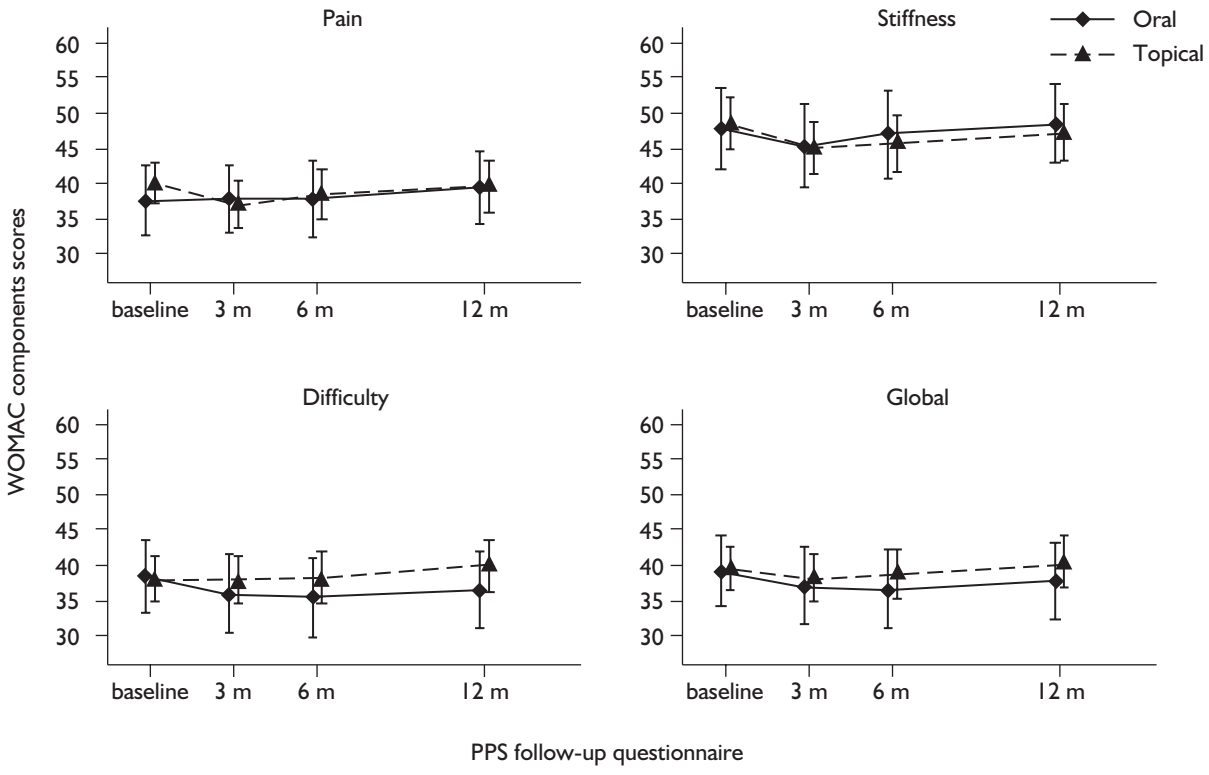
[a] End-of-study value is the last value carried forward or the 24-month follow-up. Score of zero indicates no pain, range 0–100.

difference of even borderline statistical significance in favour of oral medication (*Table 30*). Re-analysing with *t*-tests, the borderline significant results at 24 months were very similar although the *p*-values were slightly larger than 0.05. The significant effect at 24 months could be a chance finding because of multiple comparisons or a bias introduced by those ceasing to participate. Only at 24 months in the RCT did the limits of the CIs for difference in any WOMAC scores approach, or in one case (pain), exceed our predefined limits for equivalence. This may be because the smaller numbers available for this analysis resulted in wider CIs.



Data are offset only for clarity. The graphs show data only for those with a full record of pain WOMAC scores over the set time period

FIGURE 13 *WOMAC scores, RCT*



Data are offset only for clarity. The graphs show data only for those with a full record of pain WOMAC scores over the set time period

FIGURE 14 *WOMAC scores, PPS*

TABLE 29 *WOMAC mean difference, RCT: change from baseline (adjusted by regression for baseline values), topical – oral, mean difference (95% CI for difference)*

	3 months	6 months	12 months	24 months	End of study[a]
Oral/topical	133/129	128/121	125/121	80/87	139/132
Pain	–2 (–6 to 2)	1 (–3 to 5)	1 (–4 to 6)	6 (0 to 12)[b]	5 (0 to 9)[c]
Stiffness	–3 (–8 to 2)	–4 (–9 to 1)	0 (–6 to 5)	–1 (–8 to 6)	–2 (–7 to 4)
Difficulty	–2 (–5 to 2)	1 (–3 to 5)	3 (–2 to 7)	5 (–1 to 10)	3 (–2 to 7)
Global	–2 (–5 to 2)	0 (–3 to 4)	2 (–2 to 6)	4 (–1 to 10)	3 (–1 to 7)

[a] End-of-study value is the last value carried forward or the 24-month follow-up. Positive differences favour oral.
[b] $p = 0.049$.
[c] $p = 0.042$.

TABLE 30 *WOMAC mean difference, PPS: change from baseline (adjusted by regression for baseline values), topical – oral, mean difference (95% CI for difference)*

	3 months	6 months	12 months	24 months	End of study[a]
Topical/oral	71/198	66/194	70/184	65/162	75/209
Pain	–2 (–7 to 3)	–2 (–7 to 3)	–1 (–7 to 4)	0 (–6 to 6)	–1 (–7 to 5)
Stiffness	0 (–6 to 6)	–3 (–9 to 3)	–2 (–8 to 4)	–2 (–9 to 5)	–3 (–9 to 3)
Difficulty	2 (–3 to 6)	3 (–2 to 7)	2 (–3 to 7)	1 (–5 to 7)	1 (–4 to 6)
Global	1 (–3 to 5)	1 (–3 to 5)	1 (–4 to 6)	0 (–6 to 6)	0 (–5 to 5)

[a] End-of-study value is the last value carried forward or the 24-month follow-up. Positive differences favour oral.

Major adverse effects

The rates for unplanned hospital admissions during the study period were low. There were no significant differences between the topical and oral groups in either study (*Tables 31–36*). There were two deaths in the PPS topical group and no deaths in the RCT at the end of the study. The causes of death were prostate cancer and subarachnoid haemorrhage. In the RCT, 16 participants had a total of 22 unplanned admissions and in the PPS 25 participants had 29 unplanned admissions (*Tables 31* and *32*). These data do not indicate any differences in the rate of serious adverse effects in either study (*Tables 31–37*).

Minor adverse effects

There were few differences in the incidences of gastrointestinal, renovascular and respiratory adverse effects, defined using our Delphi study, between oral and topical preparation groups in either the RCT or the PPS (*Tables 38–43*).

TABLE 31 *Number and rate of first unplanned hospital admission, RCT*

	Oral *n* = 140	Topical *n* = 136	Difference in rates topical – oral (95% CI)[a]
0–12 months	2 (1.4)	6 (4.5)	3.1 (–1.0 to 7.2), $p = 0.16$
0–18 months	5 (2.5)	9 (4.8)	2.3 (–1.6 to 6.1), $p = 0.27$
0–24 months	6 (2.6)	10 (4.6)	2.0 (–1.5 to 5.5), $p = 0.28$

[a] Per 100 person years of exposure.

TABLE 32 *Number and rate of first unplanned hospital admission, PPS*

	Oral *n* = 77	Topical *n* = 220	Difference in rates topical – oral (95% CI)[a]
0–12 months	4 (5.2)	11 (5.1)	–0.1 (–6.1 to 5.8), $p = 0.93$
0–18 months	5 (4.5)	15 (4.8)	0.3 (–4.3 to 4.9), $p = 0.92$
0–24 months	6 (4.3)	19 (4.9)	0.6 (–3.5 to 4.7), $p = 0.81$

[a] Per 100 person years of exposure.

TABLE 33 *Major adverse effects, RCT (up to 24 months or end of study if earlier)*

	Oral *n* = 140	Topical *n* = 136	Topical – oral (95% CI)
Deaths	0 (0%)	0 (0%)	0%, $p = 1$
Any episode of gastric bleeding	0 (0%)	0 (0%)	0%, $p = 1$
Emergency hospital admission (any reason)	6 (4%)	10 (7%)	3.1% (–2.5 to 8.6%)

TABLE 34 *Major adverse effects, PPS (up to 24 months or end of study if earlier)*

	Oral *n* = 78	Topical *n* = 220	Topical – oral (95% CI)
Deaths	0	2 (1%)	0.9%, $p = 1.0$
Any episode of gastric bleeding	1 (1%)[a]	0	–1.3%, $p = 0.27$
Unplanned hospital admission (any reason)	6 (8%)	19 (9%)	0.9 (–6.0 to 7.9%)

[a] Participant had upper gastrointestinal bleed when already in hospital for a planned admission.

TABLE 35 *Unplanned admissions by category, RCT*

Category	Oral *n* = 144		Topical *n* = 138	
	No. of admissions	No. of participants	No. of admissions	No. of participants
Cardiovascular	8	5	4	4
Other	2	2	8	6
Total	10	6[a]	12	10

[a] One participant was admitted in more than one category.

TABLE 36 *Unplanned admissions by category, PPS*

Category	Oral *n* = 79		Topical *n* = 224	
	No. of admissions	No. of participants	No. of admissions	No. of participants
Cardiovascular	2	1	8	7
Other	5	5	13	11
Total	7	6	21	18

TABLE 37 *Detailed breakdown of cardiovascular and chest pain admissions*

	RCT		PPS	
	Oral *n* = 140	Topical *n* = 136	Oral *n* = 77	Topical *n* = 220
Chest pain	3[a] (2%)	1 (1%)	1[b] (1%)	1[c] (<1%)
Heart failure	0	0	0	1 (<1%)
Other vascular	2 (1%)	1 (1%)	0	4 (2%)
Arrhythmia	0	2 (1%)	0	2[c] (1%)

[a] One participant admitted four times.
[b] One participant admitted twice with chest pain.
[c] One participant admitted once with chest pain and once with arrhythmia.

The exceptions were in the RCT, where the oral group had more new diagnoses of asthma and more participants with a >15% reduction in their peak expiratory flow rate compared with the topical group. This translated into 9% (95% CI 2% to 17%) more participants in the oral group having at least one of our defined respiratory adverse effects (*Tables 38* and *39*). In the PPS, if all bloods taken during the study are considered, 6% of participants in the topical group had a fall in Hb of ⩾1.6 g compared with none in the oral group ($p = 0.41$). This did not translate into a difference in the number of participants having one or more defined gastrointestinal adverse effects.

Although there was a statistically significant difference in defined respiratory adverse effect, rate, this did not translate into an overall difference in the total number of participants having one or more defined adverse effect (*Tables 38–45*). In addition to the analysis of defined adverse effects, a prespecified analysis was performed of the mean difference in our clinical and laboratory measurements. The only statistically significant difference in these analyses was that those randomised to the oral group had a less favourable change in creatinine levels at 12 months (–3.7 mmol/l, 95% CI –7.0 to –0.9) (*Tables 46* and *47*).

TABLE 38 *Defined gastrointestinal adverse effects by or at 12 months, RCT*

	***N* (%)[a]**		**Difference topical – oral (95% CI)**
	Oral *n* = 144	**Topical *n* = 138**	
Dyspepsia: from 3, 6 and 12 months questionnaires[b]	*n* = 139	*n* = 133	
Indigestion increased by one or more categories from baseline	54 (39%)	50 (38%)	–1.3 (–24 to 20%)
Indigestion more than occasionally, or worse, but not increased from baseline by that point	3 (2%)	2 (2%)	–0.7%, *p* = 1
Rate to first of either of the above to 12-months *N* (rate per 100 person years) (95% CI for difference in rate)	56 (52)	51 (49)	–3.6 (–23 to 16)
Bloods collected as part of TOIB[c]			
Ferritin below normal range	4 (3%)	6 (4%)	2.4%, *p* = 0.52
Hb <11.3 (males), <10.6 (females)	0 (0%)	0 (0%)	0%, *p* = 1
Hb reduction ⩾1.6 g	1 (<%)	3 (2%)	2.0%, *p* = 0.34
Any of above	5 (4%)	8 (6%)	3.4%, (–2.7 to 9.7%)
Any blood result[d]			
Ferritin below normal range	4 (3%)	6 (4%)	2.3%, *p* = 0.52
Hb <11.3 (males), <10.6 (females)	0 (0%)	1 (<1%)	0.9%, *p* = 0.47
Hb reduction ⩾1.6 g	2 (3%)	3 (2%)	1.1%, *p* = 0.67
Any of above	6 (5%)	9 (7%)	3.2% (–2.8 to 9.3%)
Any gastrointestinal adverse effect by 12 months:[b] *N* (%)	57 (40%)	58 (42%)	2.5% (–9 to 14%)
Any defined gastrointestinal adverse effect by 12 months (rate per 100 person years)[b] (95% CI for difference in rate)	49	54	4.3 (–14 to 23)

[a] Unless stated otherwise.
[b] Only the first adverse effect is counted.
[c] 12-month planned TOIB blood test if within 18 months of study entry.
[d] If 12-month blood test present, data show any adverse effect up to this point. If no 12-month blood test present, data show any adverse effect up to 18 months.

TABLE 39 *Defined gastrointestinal adverse effects by or at 12 months, PPS*

	***N* (%)[a]**		**Difference in proportions topical – oral (95% CI)**
	Oral *n* = 79	**Topical *n* = 224**	
Dyspepsia: from 3, 6 and 12 months questionnaires[b]	*n* = 77	*n* = 211	
Indigestion increased by one or more category from baseline	26 (34%)	69 (33%)	–1.1 (–13 to 11%)
Indigestion more than occasionally or worse but not increased from baseline by that point	1 (1%)	3 (1%)	0.1%, *p* = 0.99
Rate to either of the above to 12 months			
N (rate per 100 person years) (95% CI for difference in rate)	27 (44)	71 (42)	–1.5 (–21 to 18)
Bloods collected as part of TOIB[c]			
Ferritin below normal range	4 (6%)	5 (2.6%)	–2.6%, *p* = 0.25
Hb <11.3 (males), <10.6 (females)	0 (0%)	1 (<1%)	0.5%, *p* = 0.99
Hb reduction ⩾1.6 g	0 (0%)	6 (3%)	3.1%, *p* = 0.04
Any of above	4 (6%)	12 (6%)	3.5% (–2.7 to 9.7%)
Any blood result[d]			
Ferritin below normal range	4 (5.8%)	6 (2.6%)	–3.2%, *p* = 0.46
Hb <11.3 (males), <10.6 (females)	0 (0%)	2 (1.0%)	1.0%, *p* = 0.99
Hb reduction ⩾1.6 g	0 (0%)	12 (5.9%)	5.9%, *p* = 0.04
Any of above	4 (5.7%)	17 (8.3%)	2.5% (–4.1 to 9.1%)
Any defined gastrointestinal adverse effect by 12-months: *N* (%)	29 (38%)	82 (37%)	–1% (–13 to 12%)
Any defined gastrointestinal adverse effect by 12 months (rate per 100 person years) (95% CI for difference in rate)	29 (44)	82 (45%)	0.1 (–19 to 19)

[a] Unless stated otherwise.
[b] Only the first adverse effect is counted.
[c] 1-year planned TOIB blood test if within 18 months of study entry.
[d] If 12-month blood test present, data show any adverse effect up to this point. If no 12-month blood test present, data show any adverse effect up to 18 months.

Renovascular

TABLE 40 *Defined renovascular adverse effects at 12 months, RCT*

	N (%)		Differences in proportions topical – oral (95% CI)
	Oral n = 144	**Topical n = 138**	
New diagnosis of heart failure	*n* = 140 0 (0%)	*n* = 136 2 (1%)	1.5%, *p* = 0.24
Blood pressure at 12 months	*n* = 120	*n* = 114	
Increase in systolic BP ⩾20 mmHg	13 (11%)	15 (13%)	2.3% (–6.0 to 10.7%)
Increase in diastolic BP ⩾10 mmHg	9 (8%)	7 (6%)	–1.4% (–7.8 to 5.1%)
Bloods collected as part of TOIB[a]	*n* = 121	*n* = 105	
Creatinine >152 mmol/l	0 (0%)	0 (0%)	0%, *p* = 0.99
Increase in creatinine ⩾20 mmol/l	6 (5%)	2 (2%)	–3.1%, *p* = 0.29
Any blood result[b]	*n* = 132	*n* = 115	
Creatinine >152 mmol/l	0 (0%)	0 (0%)	*p* = 0.99
Increase in creatinine ⩾20 mmol/l	11 (8%)	3 (3%)	–5.7 (–11.3 to –0.2%)
Any abnormal blood result	11 (8%)	3 (3%)	–5.7 (–11.3 to –0.2%)
Any defined renovascular adverse effect	22 (15%)	22 (16%)	0.8% (–7.8 to 9.4%)

[a] 12-month planned TOIB blood test if within 18 months of study entry.
[b] If 12-month blood test present, data show any adverse effect up to this point. If no 12-month blood test present, data show any adverse effect up to 18 months.

TABLE 41 *Defined renovascular adverse effects at 12-months, PPS*

	N (%)		Differences in proportions topical – oral (95% CI)
	Oral n = 79	**Topical n = 224**	
New diagnosis of heart failure	*n* = 77 0 (0%)	*n* = 220 1 (0.5%)	0.5%, *p* = 0.99
Blood pressure at 12 months	*n* = 68	*n* = 195	
Increase in systolic BP ⩾20 mmHg	5 (7%)	18 (9%)	1.93% (–5.5 to 9.3%)
Increase in diastolic BP ⩾10 mmHg	6 (9%)	18 (9%)	–1.4% (–7.8 to 5.1%)
Blood results at 12 months taken for TOIB[a]	*n* = 69	*n* = 194	
Creatinine >152 mmol/l	0 (0%)	0 (0%)	0%, *p* = 0.99
Increase in creatinine ⩾20 mmol/l	4 (6%)	4 (2%)	0.4%, *p* = 0.21
Any blood result prior to or at the 12-month assessment[b]	*n* = 74	*n* = 204	
Creatinine >152 mmol/l	1 (1%)	0 (0%)	–1.4%, *p* = 0.26
Increase in creatinine ⩾20 mmol/l	5 (7%)	5 (2%)	–4.3, *p* = 0.14
Any abnormal blood result[a]	5 (6%)	5 (2%)	–4.3, *p* = 0.14
Any defined renovascular adverse effect[a]	15 (19%)	34 (15%)	–4.0 (–13.9 to 5.9%)

[a] 12-month planned TOIB blood test if within 18 months of study entry.
[b] If 12-month blood test present, data show any adverse effect up to this point. If no 12-month blood test present, data show any adverse effect up to 18 months.

Respiratory

TABLE 42 *Defined respiratory adverse effects at 12 months, RCT*

	Oral *n* = 144	**Topical *n* = 138**	**Differences in proportions topical – oral (95% CI)**
Lung function at 12 months	*n* = 122	*n* = 113	
PEF reduced by 15% or more	22 (18%)	9 (8%)	–10% (–19 to –1%)[b]
Medical record examination: *N* (rate per 100 per year)[a]	*n* = 139	*n* = 133	Differences in rate per 100 per year
New diagnosis of asthma	3 (11)	0 (0)	–11 (–24 to 1.5)
Increase in treatment for asthma/COPD	0 (0)	1 (3.0)	3 (–3 to 9)
Any defined respiratory adverse effect, *n* (%)	24 (17%)	10 (7%)	–9% (–17 to –2%)[c]

[a] The dates for new diagnoses or increase in asthma were not all available. They are all included in the 12-month table as they might have occurred by 12 months. Rates are calculated over the whole study follow-up and not to 12 months.
[b] $p = 0.023$.
[c] $p = 0.017$.

TABLE 43 *Defined respiratory adverse effects at 12 months, PPS*

	Oral *n* = 79	**Topical *n* = 224**	**Differences in proportions topical – oral (95% CI)**
Lung function at 12-months	*n* = 69	*n* = 196	
PEF reduced by 15% or more	11 (16%)	30 (15%)	–1% (–11 to 9%)
Medical record examination: *N* (rate per 100 per year)[a]	*n* = 77	*n* = 214	Differences in rate per 100 per year
New diagnosis of asthma	2 (9.0)	4 (6.7)	–2 (–16 to 11)
Increase in treatment for asthma/COPD	1 (4.5)	2 (3.4)	–1 (–11 to 9)
Any defined respiratory adverse effect, *n* (%)	14 (18%)	34 (15%)	–2.9% (–12.8 to 6.9%)

[a] The dates for new diagnoses or increase in asthma were not all available. They are all included in the 12-month table as they might have occurred by 12 months. Rates are calculated over the whole study follow-up and not to 12 months.

TABLE 44 *Summary of minor adverse effects over 12 months, RCT*

	Oral *n* = 144	**Topical *n* = 138**	**Differences in proportions topical – oral (95% CI)**
Gastrointestinal	57 (40%)	58 (42%)	2% (–9 to 14%)
Renovascular	22 (15%)	22 (16%)	1% (–8 to 9%)
Respiratory	24 (17%)	10 (7%)	–9% (–17 to –2%)[a]
Any minor adverse effect	80 (56%)	77 (56%)	0 (–11 to 12%)

[a] $p = 0.017$.

TABLE 45 *Summary of minor adverse effects over 12 months, PPS*

	Oral *n* = 79	**Topical *n* = 224**	**Differences in proportions topical – oral (95% CI)**
Gastrointestinal	29 (38%)	82 (37%)	–1% (–13 to 12%)
Renovascular	15 (19%)	34 (15%)	–4% (–14 to 6%)
Respiratory	14 (18%)	34 (15%)	–3% (–13 to 7%)
Any minor adverse effect	45 (57%)	118 (53%)	–4% (–17 to 8%)

TABLE 46 *Other measures of potential adverse effects at 12 months, RCT*[a]

	Oral *n* = 79	Topical *n* = 224	Difference topical – oral (95% CI)
Mean Hb at 12-months (SD)	14.2 (1.1)	14.1 (1.2)	–0.06 (–0.36 to 2.3)
Reduction in Hb (12 months – baseline) (SD)	0.2 (0.65)	0.7 (0.77)	0.05 (–0.13 to 0.23)
Log_e (ferritin) at 12 months (SD)	4.49 (0.86)	4.49 (0.88)	0.00 (–0.23 to 0.23)
Change in systolic blood pressure (12 months – baseline): mean (SD)	2.5 (14)	4.4 (14)	1.9 (–1.7 to 5.5)
Change in diastolic blood pressure (12 months – baseline): mean (SD)	–1.0 (8)	–0.5 (7)	0.5 (–1.3 to 2.4)
Change in serum creatinine (12 months – baseline) mean (SD)	2.4 (11)	–1.3 (10)	–3.7 (–6.5 to –0.9)[b]
Mean PEF at 12 months (SD)	380 (129)	391 (128)	11 (–22 to 44)
Change in PEF (12 months – baseline) mean (SD)	–3 (69)	4 (58)	8 (–9 to 24)
Liver function tests, ⩾3 times upper limit of normal: (*N*) (%)	3 (2.2%)	3 (2.7%)	0.4%, $p = 1$

[a] If blood was unavailable, the nearest blood to 12 months was used. Results restricted to 6–18 months of follow-up.
[b] $p = 0.011$.

TABLE 47 *Other measures of potential adverse effects at 12 months, PPS*

	Oral	Topical	Difference topical – oral (95% CI)
Mean Hb at 12 months (SD)	13.9 (1.1)	14.0 (1.3)	0.05 (–0.29 to 0.38)
Reduction in Hb (12 months – baseline) (SD)	0.01 (0.63)	0.00 (0.79)	–0.00 (–0.21 to 0.20)
Log_e (ferritin) at 12 months (SD)	4.56 (0.88)	4.45 (0.75)	–0.11 (–0.33 to 0.10)
Change in systolic blood pressure (12 months – baseline): mean (SD)	1.3 (14)	1.4 (14)	0.2 (–3.8 to 4.2)
Change in diastolic blood pressure (12 months – baseline): mean (SD)	0.6 (8)	0.3 (8)	–0.3 (–2.4 to 1.8)
Change in serum creatinine (12 months – baseline): mean (SD)	0.3 (11)	–1.7 (11)	–1.9 (–4.8 to 1.0)
Mean PEF at 12 months (SD)	364 (112)	345 (114)	–18 (–49 to 13)
Change in PEF (12 months – baseline): mean (SD)	–4 (68)	–1 (63)	3 (–15 to 20)
Liver function tests, ⩾3 times upper limit of normal: *N*(%)	2 (3%)	2 (1.%)	–1.7%, $p = 0.29$

[a] If blood was unavailable, the nearest blood to 12 months was used. Results restricted to 6–18 months of follow-up.

Secondary outcome measures

There were few differences in the secondary outcome measures between the oral and topical preparation groups in either study. There were no significant differences in the SF-36 physical component scores, troublesomeness of knee pain, overall proportion with chronic pain grade III or IV at any time-point, satisfaction with treatment, expectation and troublesome pain in other body regions at 12 months (*Figures 15–18* and *Tables 47–59*) (lower scores of SF-36 indicate worse state, range 0–100).

There were no differences in the SF-36 mental component scores in the RCT. However, there was a small difference, of borderline statistical significance, in the SF-36 mental component score at 3 months in the PPS. This may be a chance finding because of the large number of comparisons made.

There were some differences in the disability component of the chronic pain grade at 3 months and in the end-of-study analyses in the RCT. Those in the oral group had slightly less pain-related disability at 3 months and in the end-of-study analysis, but not at 12 months. There was also, after correcting for baseline differences, a difference in the odds of having chronic pain grade III or IV at 3 months and in the end-of-study assessment, but not at 12 months, the oral group doing better. This appears to be because more people got worse in the topical than in the oral group. This difference could be a consequence of fairly small changes in the component pain and disability scores. There is a suggestion from this analysis that in the RCT people in the oral group had fewer overall problems with chronic pain. Although this is a biologically plausible finding, it may be a chance observation because of the large number of

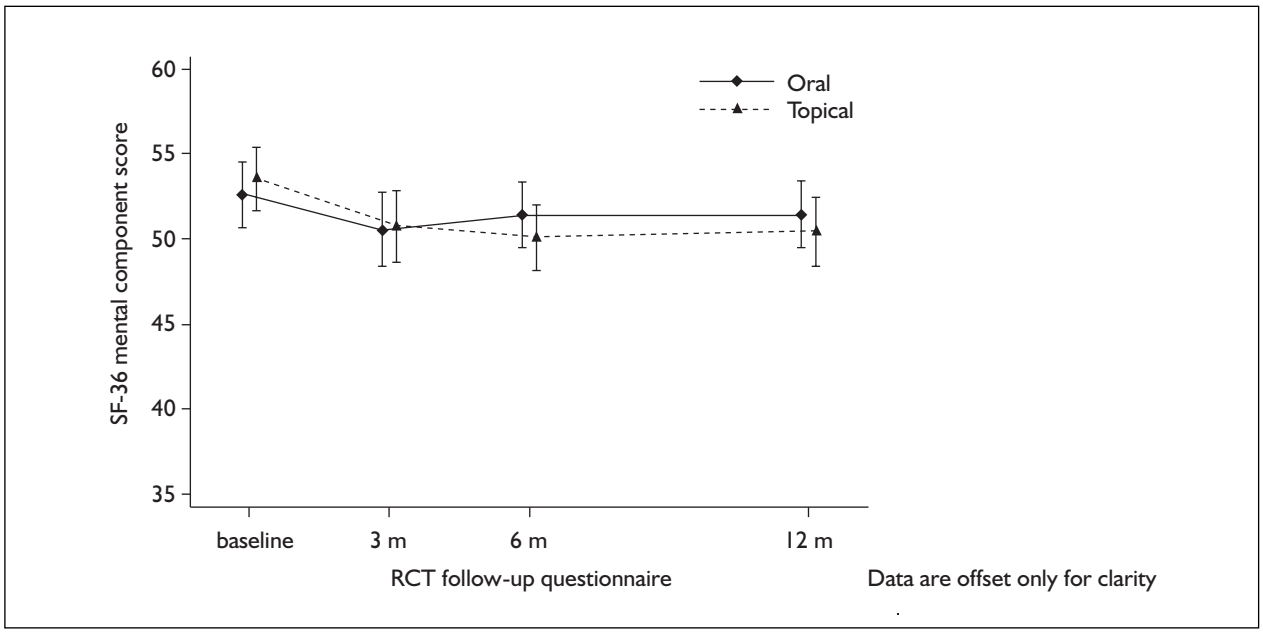


FIGURE 15 *SF-36 mental component score, RCT*

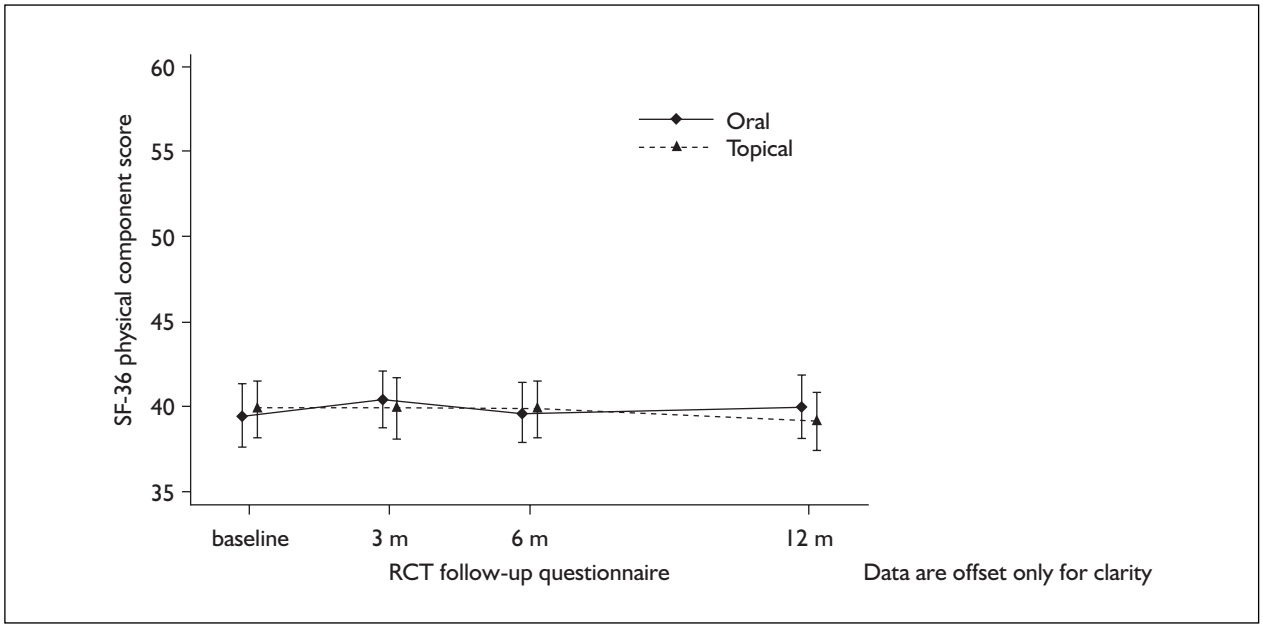


FIGURE 16 *SF-36 physical component score, RCT*

TABLE 48 *SF-36 scores[a], RCT: mean difference in change from baseline (adjusted by regression for baseline values) topical – oral, mean difference (95% CI for difference)*

	3 months	6 months	12 months	24 months	End of study[b]
n = oral/topical	123/122	118/116	115/119	72/85	127/129
Physical component score	–0.1 (–1.7 to 1.8)	–0.4 (–2.0 to 1.3)	–1.6 (–3.5 to 0.3)	–0.7 (–3.0 to 1.5)	–0.7 (–2.5 to 1.2)
Mental component score	–1.2 (–3.3 to 0.9)	–1.7 (–3.9 to 0.4)	–1.0 (–3.4 to 1.3)	–0.4 (–2.8 to 2.1)	–0.5 (–2.6 to 1.7)

[a] Lower scores of SF-36 indicate worse state. Negative values favour oral.
[b] End-of-study value is the last value carried forward or the 24-month follow-up.

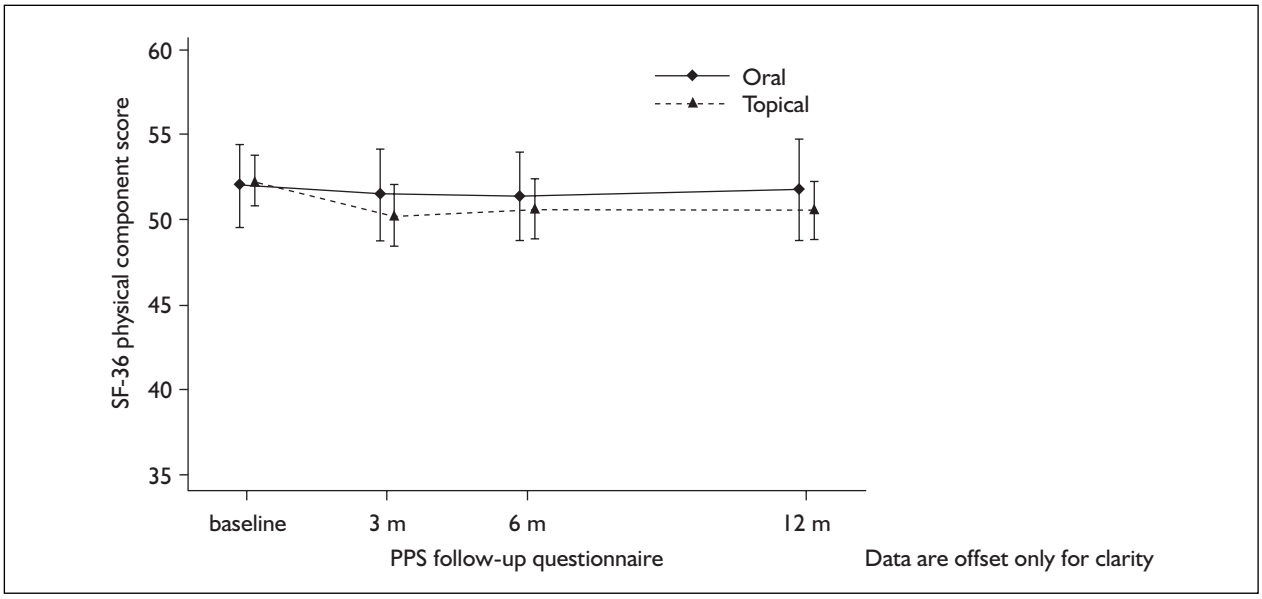


FIGURE 17 *SF-36 mental component, PPS*

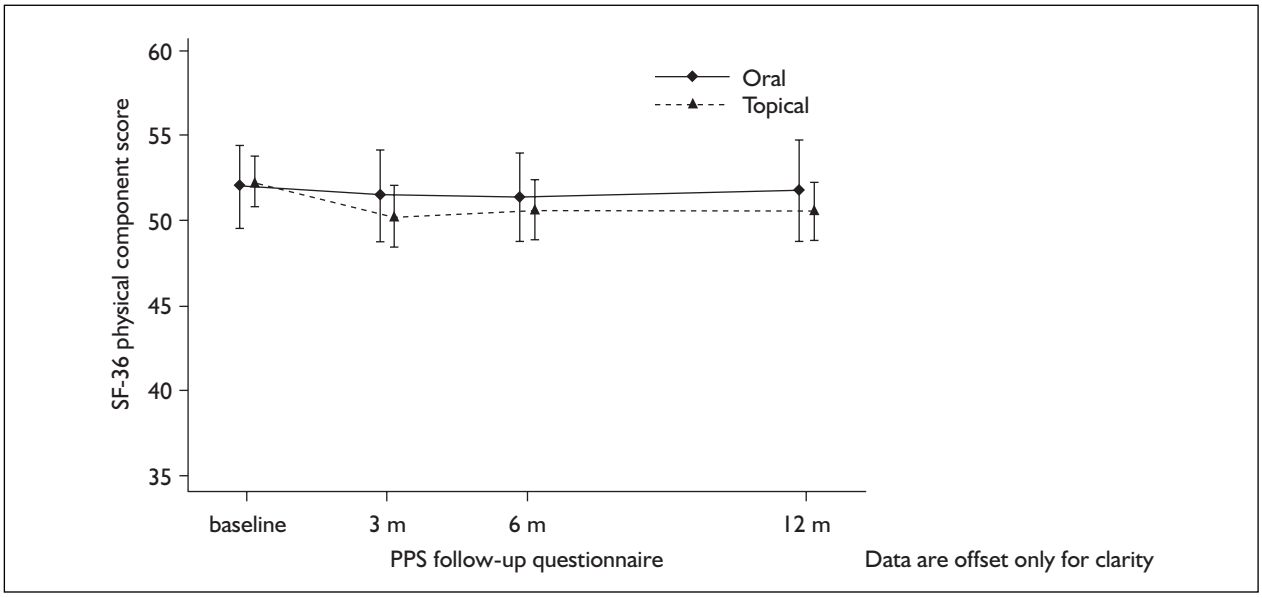


FIGURE 18 *SF-36 physical component, PPS*

TABLE 49 *SF-36 scores[a], PPS: mean difference in change from baseline (adjusted by regression for baseline values) topical – oral, mean difference (95% CI for difference)*

	3 months	6 months	12 months	24 months	End of study[b]
n = oral/topical	69/179	62/177	63/169	60/143	70/189
Physical component score	0.5 (–1.2 to 2.1)	0.8 (–1.2 to 2.7)	0.0 (–2.0 to 1.9)	–0.6 (–2.8 to 1.6)	0.4 (–1.6 to 2.3)
Mental component score	–2.4 (–4.8 to –0.1)[c]	–0.5 (–2.9 to 1.9)	–0.3 (–2.7 to 2.0)	–1.8 (–4.4 to 0.9)	–1.1 (–3.5 to 1.3)

[a] Negative values favour oral.
[b] End-of-study value is the last value carried forward or the 24-month follow-up.
[c] $p = 0.043$.

TABLE 50 *Chronic pain grade,[a] RCT*

	Baseline	3 months	6 months	12 months	24 months	End of study
n = oral/topical	142/137	133/129	126/120	124/121	81/87	139/132
Pain intensity						
Oral (SD)	53 (20)	49 (21)	49 (22)	47 (21)	46 (21)	48 (21)
Topical(SD)	52 (18)	51 (19)	50 (21)	49 (22)	50 (21)	51 (22)
Disability						
Oral (SD)	38 (27)	34 (24)	34 (25)	32 (25)	34 (25)	34 (26)
Topical (SD)	35 (23)	36 (25)	34 (26)	34 (26)	35 (25)	37 (26)
Proportion grade III/IV	141/136	132/129	126/119	124/121	80/87	138/132
Oral	50 (35%)	31 (24%)	32 (25%)	35 (28%)	20 (25%)	35 (25%)
Topical	35 (26%)	39 (30%)	28 (24%)	34 (28%)	31 (36%)	45 (34%)

[a] Chronic pain grade is calculated from two components, a pain score and a disability score. In addition to the chronic pain grade scores we have presented the mean pain and disability scores.

TABLE 51 *Chronic pain grade,[a] PPS*

	Baseline	3 months	6 months	12 months	24 months	End of study
n = oral/topical	79/223	73/202	69/196	70/187	76/209	76/209
Pain intensity						
Oral (SD)	55 (18)	53 (20)	49 (23)	51 (22)	52 (22)	53 (22)
Topical (SD)	52 (18)	49 (20)	47 (23)	51 (22)	51 (24)	50 (24)
Disability						
Oral (SD)	38 (23)	35 (26)	36 (27)	38 (26)	33 (24)	36 (25)
Topical (SD)	35 (26)	35 (27)	33 (27)	36 (27)	39 (29)	38 (29)
Proportion grade III/IV	78/219	72/198	69/193	70/185	66/159	75/205
Oral	26 (33%)	19 (26%)	24 (35%	22 (31%)	17 (26%)	22 (29%)
Topical	68 (31%)	59 (30%)	53 (27%)	58 (31%)	56 (35%)	70 (34%)

[a] Chronic pain grade is calculated from two components, a pain score and a disability score. In addition to the chronic pain grade scores we have presented the mean pain and disability scores.

TABLE 52 *Chronic pain grade – differences in changes from baseline, RCT: mean difference in change for topical – oral (95% CI of mean difference in change)*

	3 months	6 months	12 months	24 months	End of study
n = oral/topical	131/128	124/119	122/121	79/87	137/131
Pain intensity (95% CI difference)	0.1 (–3.8 to 4.1)	1.1 (–3.1 to 5.3)	2.1 (–2.7 to 7.0)	0.4 (–6.1 to 6.8)	2.8 (–2.2 to 7.8)
Disability (95% CI difference)	4.9 (0.2 to 9.6)[b]	4.4 (–0.9 to 9.7)[c]	4.7 (–1.2 to 10.7)	3.6 (–3.3 to 10.5)	6.5 (0.9 to 12.4)[d]
Odds ratio (95% CI) for high CPG[a]	2.3 (1.1 to 4.5)[e]	1.3 (0.7 to 2.5)	1.3 (0.7 to 2.5)	2.1 (1.0 to 4.5)[f]	2.0 (1.1 to 3.7)[g]

[a] Odds ratio of a high chronic pain grade score in patients given topical rather than oral, adjusted for status of high pain grade at baseline. Odds ratio > 1 favours oral.
[b] $p = 0.021$. [c] $p = 0.10$. [d] $p = 0.022$. [e] $p = 0.020$. [f] $p = 0.051$. [g] $p = 0.020$.

TABLE 53 *Chronic pain grade – differences in changes from baseline, PPS: mean difference in change for topical – oral (95% CI of mean difference in change)*

	3 months	6 months	12 months	24 months	End of study
n = oral/topical	73/201	69/195	70/189	67/161	76/208
Pain intensity (95% CI difference)	1.2 (–3.0 to 5.4)	2.5 (–2.6 to 7.6)	4.3 (–0.6 to 9.1)[b]	2.0 (–3.9 to 7.8)	0.4 (–4.9 to 5.7)
Disability (95% CI difference)	3.8 (–1.4 to 8.9)	0.7 (–5.1 to 6.4)	1.4 (–4.6 to 7.4)	6.5 (–0.6 to 13.5)[c]	5.2 (–1.0 to 11.3)[d]
Odds ratio (95% CI) for high CPG[a]	1.5 (0.71 to 3.2)	0.8 (0.39 to 1.6)	1.1 (0.5 to 2.1)	1.7 (0.8 to 3.4)	1.4 (0.7 to 2.7)

[a] Odds ratio of a high chronic pain grade score in patients given topical rather than oral, adjusted for status of high pain grade at baseline. Odds ratio >1 favours oral.
[b] $p = 0.084$.
[c] $p = 0.072$.
[d] $p = 0.10$.

TABLE 54 *Change in chronic pain grade from baseline (%), RCT*

	3 months	6 months	12 months	24 months	End of study[a]
Oral	*n* = 129	*n* = 123	*n* = 121	*n* = 77	*n* = 135
Worse	12	15	17	21	18
Same	58	59	56	48	48
Better	30	26	27	31	33
Topical	*n* = 127	*n* = 117	*n* = 120	*n* = 86	*n* = 130
Worse	23	27	21	33	33
Same	56	51	52	37	39
Better	21	22	28	29	28

[a] End-of-study value is the last value carried forward or the 24-month follow-up.

TABLE 55 *Change in chronic pain grade from baseline (%), PPS*

	3 months	6 months	12 months	24 months	End of study
Oral	*n* = 71	*n* = 68	*n* = 69	*n* = 65	*n* = 74
Worse	15	21	23	28	30
Same	64	56	48	45	43
Better	21	24	29	28	27
Topical	*n* = 194	*n* = 189	*n* = 181	*n* = 155	*n* = 201
Worse	25	22	28	30	27
Same	54	56	51	49	52
Better	21	22	21	21	21

TABLE 56 *Troublesomeness of knee pain, RCT*

	n (%)									
	3 months		**6 months**		**12 months**		**24 months**		**End of study**	
	Oral	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**
Not at all troublesome	1 (1)	2 (2)	2 (2)	3 (2)	4 (3)	1 (1)	4 (5)	5 (6)	4 ( )	6 (5)
Slightly troublesome	24 (18)	24 (19)	22 (17)	18 (15)	29 (23)	24 (20)	16 (20)	11 (13)	29 (21)	19 (15)
Moderately troublesome	57 (44)	60 (48)	55 (44)	51 (42)	52 (42)	48 (40)	31 (39)	28 (32)	56 (41)	46 (35)
Very troublesome	36 (27)	30 (24)	31 (25)	41 (34)	24 (19)	32 (26)	25 (31)	33 (38)	38 (28)	42 (32)
Extremely troublesome	13 (10)	10 (8)	16 (13)	8 (7)	16 (13)	16 (13)	4 (5)	10 (11)	11 (8)	18 (14)
At least moderately troublesome	106 (81)	100 (79)	102 (81)	100 (83)	92 (74)	96 (79)	60 (75)	71 (82)	105 (76)	106 (81)
Total (100%)	**131**	**126**	**126**	**121**	**125**	**121**	**80**	**87**	**138**	**131**

TABLE 57 *Troublesomeness of knee pain, PPS*

	n (%)									
	3 months		**6 months**		**12 months**		**24 months**		**End of study**	
	Oral	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**
Not at all troublesome	2 (3)	1 (<1)	1 (1)	5 (3)	1 (1)	3 (2)	4 (6)	6 (4)	4 (5)	9 (4)
Slightly troublesome	11 (15)	33 (16)	10 (15)	33 (17)	14 (20)	34 (18)	5 (8)	35 (22)	8 (11)	46 (22)
Moderately troublesome	32 (44)	77 (39)	28 (42)	80 (41)	22 (32)	71 (38)	28 (42)	51 (31)	29 (38)	66 (31)
Very troublesome	18 (25)	70 (35)	20 (30)	53 (27)	21 (30)	57 (30)	20 (30)	46 (28)	23 (30)	59 (28)
Extremely troublesome	9 (13)	20 (10)	8 (12)	25 (13)	11 (16)	24 (13)	9 (14)	24 (15)	12 (16)	30 (14)
At least moderately troublesome	59 (82)	167 (83)	56 (84)	158 (81)	54 (78)	152 (80)	57 (86)	121 (75)	64 (84)	155 (74)
Total (100%)	**72**	**201**	**67**	**196**	**69**	**189**	**66**	**162**	**76**	**210**

TABLE 58 *Troublesomeness of pain in other body areas at 12 months, RCT*

Area	Oral $n = 124$[a]	Topical $n = 121$[a]	OR[b] (95% CI)
Knee	92 (74%)	96 (79%)	1.38 (0.74 to 2.6), $p = 0.95$
Back	52 (42%)	57 (47%)	1.47 (0.80 to 2.7), $p = 0.21$
Hip/thigh	48 (40%)	42 (36%)	1.11 (0.59 to 2.1), $p = 0.74$
Shoulder/neck	44 (35%)	53 (44%)	1.41 (0.80 to 2.5), $p = 0.24$
Ankle/foot	38 (31%)	42 (35%)	1.31 (0.74 to 2.3), $p = 0.35$
Wrist/hand	40 (33%)	33 (28%)	0.99 (0.50 to 1.9), $p = 0.97$
Elbow	16 (13%)	11 (9%)	0.66 (0.27 to 1.6), $p = 0.36$
At least one moderately troublesome other than knee	93 (74%)	94 (77%)	1.16 (0.61 to 2.2), $p = 0.65$

OR, odds ratio.
[a] Number who answered the question for the back; there are slight differences for other areas, hence apparent differences in percentages.
[b] OR of being at least moderately troublesome for topical rather than oral, after adjustment for being at least moderately troublesome at baseline. OR >1 favours oral.

TABLE 59 *Troublesomeness of pain in other body areas at 12 months, PPS*

	Oral $n = 70$[a]	Topical $n = 88$[a]	OR[b] (95% CI)
Knee	54 (78%)	152 (80%)	1.32 (0.66 to 2.7), $p = 0.43$
Back	35 (50%)	88 (47%)	1.16 (0.60 to 2.2), $p = 0.65$
Hip/thigh	29 (43%)	69 (38%)	1.22 (0.62 to 2.4), $p = 0.56$
Shoulder/neck	32 (46%)	88 (47%)	1.17 (0.59 to 2.4), $p = 0.65$
Ankle/foot	29 (41%)	67 (37%)	0.98 (0.51 to 1.9), $p = 0.94$
Wrist/hand	24 (34%)	57 (31%)	1.10 (0.54 to 2.3), $p = 0.78$
Elbow	14 (20%)	24 (13%)	0.97 (0.40 to 2.3), $p = 0.95$
At least one moderately troublesome other than knee	56 (80%)	149 (79%)	1.26 (0.60 to 2.6), $p = 0.54$

[a] Number who answered the question for the back; there are slight differences for other areas, hence apparent differences in percentages.
[b] OR of being at least moderately troublesome for topical rather than oral, after adjustment for being at least moderately troublesome at baseline. OR >1 favours oral.

TABLE 60 *Satisfaction*[a] *with treatment, measured at 12 months*

	Oral	Topical	Topical – oral (95% CI)
RCT	$n = 114$	$n = 115$	
Mean (SD)	6.5 (3.2)	5.7 (3.1)	–0.8 (–1.7 to –0.0)[b]
Median (IQR)	8 (4, 9)	6 (4, 8)	
PPS	$n = 66$	$n = 179$	
Mean (SD)	6.1 (3.1)	6.3 (3.0)	0.2 (–0.6 to 1.1)[c]
Median (IQR)	7 (4, 9)	7 (5, 9)	
Difference in means of satisfaction (PPS – RCT)			
Difference in means (95% CI)	–0.4 (–1.3 to 0.5), $p = 0.38$	0.6 (–0.1 to 1.3), $p = 0.087$	

IQR, interquartile range.
[a] Measured on a scale of 0–10: 0 not at all satisfied, 10 completely satisfied.
[b] $p = 0.046$. After adjusting for baseline expectations there was a similar reduction but of borderline statistical significance –0.8 points (95% CI –1.6 to 0.05), $p = 0.064$.
[c] $p = 0.62$.

comparisons made, particularly as few of the other measures show any differences between the two groups. It should also be noted that the chronic pain grade measures pain over the preceding 6 months; hence the 3-month data will be partially reflecting pain levels prior to joining the study.

In the RCT, participants in the oral group had slightly higher satisfaction with their knee pain, of borderline statistical significance, compared with those in the topical group; however, this difference was not statistically significant after correcting for baseline differences (*Table 60*). In the PPS there were no differences in participants' satisfaction between the two groups. Comparing satisfaction between the two studies, no differences were found between the two oral groups or the two topical groups or in a comparison of all of those in the RCT with all of those in the PPS (RCT, $p = 0.31$; PPS, $p = 0.58$; one-way analysis of variance).

Medication use

Good MR data were obtained on the number of drugs prescribed during the follow-up period, with complete data on 90% of participants in the RCT and 94% of participants in the PPS. The different follow-up periods between the two studies will affect the interpretation of the 12–24-month data. Therefore, presented here are just the data on the number of DDDs of different drug groups used up to 12 months, the time-frame of the primary analysis. Standard DDD values were used for all drugs with the exception of topical NSAIDs, where a DDD was defined as 1.5 g/day and aspirin, where a low-dose cardiovascular DDD (75 mg/day) was used rather than a high-dose analgesic DDD of 3000 mg/day.

The data are presented as DDDs prescribed in each quarter after joining the study and the total number of DDDs prescribed in each year. This allows some interpretation of changes over time. The proportion of people using drugs from each group and the mean number of DDDs for all participants are presented. Initial starter packs of topical (24 DDDs) or oral (eight DDDs) ibuprofen have not been included in these analyses.

Our *a priori* definition of adherence was that participants should be taking more DDDs of NSAID by their allocated route than by the alternative route. Subsequently, because of the additional use of other painkillers, we decided to estimate adherence using a stricter definition. To be adherent a participant needed to take the same or more DDDs of NSAID via their allocated route than the total number of DDDs of NSAID by an alternative route and DDDs of 'rescue medications' (paracetamol, mild and strong opioids). Thus, participants taking no painkilling drugs at all were considered adherent to treatment. An additional category of adherence to ibuprofen and route (the original prescription) was also considered. This was defined similarly: adherents needed to take the same or more DDDs of ibuprofen via their allocated route than all other painkillers.

RCT

NSAIDs overall use

During the 12 months of follow-up, 92% of those in the oral group had a prescription for an oral NSAID and only 5% a prescription for a topical NSAID. In contrast, in the topical group, 83% had a prescription for a topical NSAID and 37% a prescription for an oral NSAID. In the topical group, fewer than half as many people had a prescription for oral ibuprofen (11%) as for another NSAID (29%). This pattern is repeated when the mean number of DDDs prescribed is considered (*Tables 61–64*). The higher use of oral NSAIDs in the topical group concurs with participant self-report. These 12-month data conceal some change of use over time. In quarter one, 83% of those in the oral group were prescribed an oral NSAID, whereas by quarter four this had fallen to just 46%. These prescribing rates may not reflect true usage because in the 3 months prior to the 12-month questionnaire approximately 10% of those reporting that they had taken NSAIDs via their allocated route in the previous month had not actually had a prescription for them in the previous 3 months; but this still indicates that, even within a trial, many people do not go on using oral NSAIDs in the long term. A similar but more striking pattern in seen in the topical groups, where the proportion issued a prescription for a topical NSAID fell from 80% in quarter one to just 29% in quarter four. *Figure 19* plots the distribution of number of DDDs of oral NSAIDs prescribed just for those participants who had at least one prescription. The width of each bar represents 30 days' supply. It can be seen that in the oral group there is a wide range of usage, with most of these participants using less than 3 months' worth of oral ibuprofen; median days supply, ibuprofen 84, all NSAIDs 112 days. A substantial minority were prescribed 6–15 months' supply over a 12-month period. Those in the topical group who used oral NSAIDs typically used less than 1 month's worth of oral ibuprofen. Similar graphs for the topical group show that more DDDs of

TABLE 61 *Number of users and percentage of all participants with prescription records in the 12 months of follow-up in the RCT (oral/topical* n *= 130/124)*

	1st quarter		2nd quarter		3rd quarter		4th quarter	
Category	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**
Oral ibuprofen	105 (81)	4 (3)	61 (47)	5 (4)	58 (45)	8 (6)	49 (38)	7 (6)
Other oral NSAIDs	10 (8)	20 (16)	19 (15)	21 (17)	16 (12)	21 (17)	13 (10)	23 (19)
All oral NSAIDs	**108 (83)**	**23 (19)**	**76 (58)**	**26 (21)**	**73 (56)**	**28 (23)**	**60 (46)**	**29 (23)**
Topical ibuprofen	3 (2)	98 (79)	1 (1)	56 (45)	2 (2)	42 (34)	0 (0)	36 (29)
Other topical NSAIDs	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)
All topical NSAIDs	3 (2)	99 (80)	1 (1)	56 (45)	3 (2)	42 (34)	1 (1)	36 (29)
Other topical drugs	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Paracetamol	25 (19)	33 (27)	24 (18)	29 (23)	26 (20)	33 (27)	29 (22)	25 (20)
Mild opioids	8 (6)	2 (2)	6 (5)	2 (2)	7 (5)	3 (2)	10 (8)	2 (2)
Strong opioids	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
All 'rescue medication'	**30 (23)**	**35 (28)**	**29 (22)**	**31 (25)**	**31 (24)**	**35 (28)**	**35 (27)**	**28 (23)**
Cardiovascular drugs	51 (39)	38 (31)	51 (39)	37 (30)	52 (40)	38 (31)	53 (41)	41 (33)
Aspirin	19 (15)	12 (10)	21 (16)	9 (7)	24 (18)	10 (8)	24 (18)	11 (9)
Indigestion drugs	10 (8)	17 (14)	16 (12)	16 (13)	12 (9)	16 (13)	15 (12)	16 (13)
Respiratory drugs	4 (3)	4 (3)	4 (3)	5 (4)	3 (2)	5 (4)	5 (4)	4 (3)

TABLE 62 *Mean and SD of days' worth of drugs prescribed for all participants with prescription data in the 12 months of follow-up in the RCT (oral/topical* n *= 130/124)*

	1st quarter		2nd quarter		3rd quarter		4th quarter	
Category	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**
Oral ibuprofen	45 (35)	2 (15)	23 (30)	2 (11)	22 (30)	3 (12)	16 (24)	2 (9)
Other oral NSAIDs	5 (21)	12 (33)	10 (28)	12 (32)	10 (30)	13 (35)	8 (29)	14 (34)
All oral NSAIDs	**51 (38)**	**15 (35)**	**33 (37)**	**14 (33)**	**32 (37)**	**16 (36)**	**24 (34)**	**16 (35)**
Topical ibuprofen	3 (24)	89 (83)	1 (6)	49 (75)	1 (8)	42 (76)	0 (0)	30 (58)
Other topical NSAIDs	0 (0)	1 (7)	0 (0)	0 (0)	2 (18)	0 (0)	1 (12)	0 (0)
All topical NSAIDs	**3 (24)**	**90 (83)**	**1 (6)**	**49 (75)**	**3 (19)**	**42 (76)**	**1 (12)**	**30 (58)**
Other topical drugs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Paracetamol	6 (20)	9 (19)	7 (20)	7 (18)	9 (24)	9 (19)	9 (22)	7 (17)
Mild opioids	3 (14)	0 (4)	3 (15)	1 (6)	3 (17)	1 (5)	4 (16)	1 (7)
Strong opioids	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
All 'rescue medication'	**9 (26)**	**9 (19)**	**10 (28)**	**8 (19)**	**12 (32)**	**9 (20)**	**13 (30)**	**8 (19)**
Cardiovascular drugs	61 (115)	45 (104)	63 (113)	43 (93)	72 (136)	47 (99)	68 (122)	46 (96)
Aspirin	12 (32)	8 (28)	12 (30)	6 (25)	19 (47)	7 (27)	15 (41)	7 (28)
Indigestion drugs	5 (18)	6 (18)	8 (24)	6 (21)	7 (25)	7 (25)	7 (22)	7 (22)
Respiratory drugs	4 (28)	3 (17)	5 (37)	4 (25)	5 (41)	6 (42)	4 (28)	3 (20)

topical ibuprofen were prescribed over the first year, most had less than 6 months' supply of topical medication; median 133 days. A small number of participants were supplied with more than 1.5 years' worth of DDDs of topical NSAID over a 1-year period (*Figures 20–24*).

By quarter four, the mean number of DDDs of oral NSAID prescribed in the oral group was 24, whereas in the topical group it was 16; the percentage taking any oral NSAID was twice as high in the oral as in the topical group. This is consistent with the mean DDDs of oral NSAIDs amongst users, which is 68 (SD = 42) in the oral group compared with 152 (SD = 113) in the topical group. This could be expected if we assume that those changing to oral from topical include more participants who have more severe pain, that is, pain not treated adequately by the topical treatment.

NSAID adherence

The difference in adherence to NSAID in the RCT masks some similarities between the groups. There are virtually identical proportions in each quarter who were prescribed no painkilling drugs.

TABLE 63 *Medications prescribed over 12-months of follow-up in RCT (oral/topical* n *= 130/124)*

	Participants prescribed medication (%) in year 1			Mean (SD) prescriptions per participants in year 1		
Category	**Oral**	**Topical**	**95% CI difference**	**Oral**	**Topical**	**95% CI difference**
Oral ibuprofen	115 (88%)	14 (11%)	–85 to –69%	106 (97)	9 (41)	–115 to –78
Other oral NSAIDs	23 (18%)	36 (29%)	1 to 22%	33 (92)	52 (121)	–8 to 45
All oral NSAIDs	**119 (92%)**	**46 (37%)**	**–64 to 45%**	**139 (116)**	**61 (126)**	**–109 to –49**
Topical ibuprofen	5 (4%)	102 (82%)	71 to 86%	4 (27)	211 (249)	163 to 250
Other topical NSAIDs	1 (1%)	1 (1%)	–2 to 2%	3 (n/a)	1 (n/a)	–7 to 3
All topical NSAIDs	**6 (5%)**	**103 (83%)**	**71 to 86%**	**7 (40)**	**211 (249)**	**161 to 248**
Other topical drugs	3 (2%)	3 (2%)	–4 to 4%	3 (17)	1 (7)	–5 to 2
Paracetamol	47 (36%)	55 (44%)	–4 to 20%	31 (78)	31 (64)	–17 to 18
Mild opioids	16 (12%)	4 (3%)	–16 to –3%	12 (60)	3 (21)	–21 to 2
Strong opioids	0 (0%)	1 (1%)	–1 to 2%	0 (0)	0 (0)	0 to 0
All 'rescue medication'	**55 (42%)**	**57 (46%)**	**–9 to 16%**	**43 (107)**	**34 (67)**	**–31 to 13**
Cardiovascular drugs	58 (45%)	46 (37%)	–20 to 5%	265 (448)	181 (355)	–183 to 17
Aspirin	25 (19%)	16 (13%)	–15 to 3%	58 (130)	28 (101)	–59 to –1
Indigestion drugs	21 (16%)	27 (22%)	–4 to 15%	26 (81)	27 (78)	–19 to 20
Respiratory drugs	5 (4%)	8 (6%)	–3 to 8%	19 (132)	16 (87)	–31 to 25

TABLE 64 *Number of users and percentage of all patients with prescription records in the 12 months of follow-up in the PPS (oral/topical* n *= 76/210)*

	1st quarter		2nd quarter		3rd quarter		4th quarter	
Category	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**
Oral ibuprofen	55 (72)	8 (4)	43 (57)	13 (6)	39 (51)	12 (6)	36 (47)	10 (5)
Other oral NSAIDs	5 (7)	17 (8)	4 (5)	17 (8)	11 (14)	21 (10)	12 (16)	17 (8)
All oral NSAIDs	**57 (75)**	**25 (12)**	**46 (61)**	**30 (14)**	**46 (61)**	**32 (15)**	**47 (62)**	**27 (13)**
Topical ibuprofen	0 (0)	154 (73)	0 (0)	98 (47)	0 (0)	91 (43)	0 (0)	69 (33)
Other topical NSAIDs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
All topical NSAIDs	**0 (0)**	**154 (73)**	**0 (0)**	**98 (47)**	**0 (0)**	**91 (43)**	**0 (0)**	**69 (33)**
Other topical drugs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Paracetamol	26 (34)	53 (25)	25 (33)	58 (28)	22 (29)	55 (26)	24 (32)	56 (27)
Mild opioids	2 (3)	5 (2)	4 (5)	8 (4)	2 (3)	11 (5)	6 (8)	8 (4)
Strong opioids	0 (0)	1 (0)	1 (1)	2 (1)	0 (0)	1 (0)	2 (3)	1 (0)
All 'rescue medication'	**27 (36)**	**57 (27)**	**27 (36)**	**63 (30)**	**23 (30)**	**61 (29)**	**27 (36)**	**63 (30)**
Cardiovascular drugs	24 (32)	69 (33)	25 (33)	73 (35)	26 (34)	71 (34)	28 (37)	72 (34)
Aspirin	13 (17)	30 (14)	13 (17)	34 (16)	11 (14)	30 (14)	13 (17)	31 (15)
Indigestion drugs	7 (9)	19 (9)	5 (7)	22 (10)	4 (5)	21 (10)	6 (8)	22 (10)
Respiratory drugs	3 (4)	18 (9)	4 (5)	20 (10)	3 (4)	20 (10)	6 (8)	26 (12)

Similarly, those who are adherent to their original prescriptions of oral or topical ibuprofen in the fourth quarter are also similar: 29% versus 26% in the RCT.

The difference in adherence to NSAID arises because 9% of the RCT oral group have changed the balance of their painkillers from ibuprofen to another NSAID, whereas none of the topical group are using enough of a different topical NSAID to affect the difference in adherence to NSAID or ibuprofen. The only statistically significant difference is between the topical and oral adherence to NSAID in the third quarter, difference = 18% (95% CI 8 to 28%), $p = 0.0007$.

Other drugs

There are few obvious differences in the prescribing rates for other drugs. Importantly, there was no significant difference in the average number of DDDs of 'rescue medication' (paracetamol and opioids) prescribed in the first 12 months of follow-up (oral 43 versus topical 34 DDDs). Most of those who used 'rescue

TABLE 65 *Mean and SD of days' worth of drugs prescribed for all patients with prescription data in the first 12 months of follow-up in the PPS (oral/topical* n *= 76/210)*

	1st quarter		2nd quarter		3rd quarter		4th quarter	
Category	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**	**Oral**	**Topical**
Oral ibuprofen	43 (35)	2 (11)	28 (31)	3 (15)	32 (39)	2 (10)	24 (32)	2 (13)
Other oral NSAIDs	5 (21)	4 (16)	4 (19)	4 (15)	10 (29)	6 (24)	11 (34)	4 (17)
All oral NSAIDs	**48 (39)**	**6 (19)**	**32 (33)**	**7 (21)**	**43 (43)**	**9 (26)**	**36 (41)**	**7 (21)**
Topical ibuprofen	0 (0)	97 (101)	0 (0)	58 (84)	0 (0)	53 (83)	0 (0)	38 (67)
Other topical NSAIDs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
All topical NSAIDs	**0 (0)**	**97 (101)**	**0 (0)**	**58 (84)**	**0 (0)**	**53 (83)**	**0 (0)**	**38 (67)**
Other topical drugs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Paracetamol	8 (14)	8 (17)	9 (16)	8 (16)	11 (22)	9 (21)	11 (20)	8 (19)
Mild opioids	2 (17)	1 (10)	2 (11)	1 (10)	2 (17)	2 (14)	3 (18)	2 (12)
Strong opioids	0 (0)	0 (1)	0 (1)	0 (1)	0 (0)	0 (0)	0 (2)	0 (0)
All 'rescue medication'	**10 (21)**	**9 (19)**	**11 (20)**	**9 (18)**	**13 (27)**	**12 (25)**	**15 (28)**	**10 (22)**
Cardiovascular drugs	50 (130)	65 (128)	55 (107)	65 (133)	65 (144)	67 (128)	75 (165)	59 (118)
Aspirin	13 (34)	14 (40)	16 (38)	17 (43)	13 (32)	15 (42)	13 (31)	15 (43)
Indigestion drugs	6 (28)	3 (12)	3 (16)	4 (13)	4 (18)	5 (18)	5 (21)	5 (18)
Respiratory drugs	5 (36)	10 (59)	12 (76)	8 (36)	24 (190)	11 (48)	34 (202)	13 (49)

TABLE 66 *Medications prescribed over 12 months in PPS (oral/topical* n *= 76/210)*

	Participants prescribed medication (%) in 12 months			Mean (SD) prescriptions per participants in 12 months		
Category	**Oral**	**Topical**	**95% CI difference**	**Oral**	**Topical**	**95% CI difference**
Oral ibuprofen	63 (83%)	22 (10%)	–82 to –63%	128 (113)	10 (43)	–137 to –101
Other oral NSAIDs	17 (22%)	35 (17%)	–16 to 5%	31 (84)	18 (62)	–30 to –6
All oral NSAIDs	**67 (88%)**	**55 (26%)**	**–71 to –53%**	**159 (132)**	**28 (73)**	**–155 to –107**
Topical ibuprofen	0 (0%)	170 (81%)	76 to 86%	0 (0)	245 (279)	182 to 308
Other topical NSAIDs	0 (0%)	0 (0%)	NA	0 (0)	0 (0)	NA
All topical NSAIDs	**0 (0%)**	**170 (81%)**	**76 to 86%**	**0 (0)**	**245 (279)**	**182 to 308**
Other topical drugs	3 (4%)	3 (1%)	–7 to 2%	11 (68)	1 (10)	–19 to –0.3
Paracetamol	38 (50%)	80 (38%)	–25 to 1%	40 (64)	33 (63)	–24 to 10
Mild opioids	8 (11%)	15 (7%)	–11 to 4%	10 (61)	7 (43)	–15 to 10
Strong opioids	2 (3%)	2 (1%)	–6 to 2%	0 (3)	0 (2)	–1 to 0.3
All 'rescue medication'	**40 (53%)**	**84 (40%)**	**–26 to 0.4%**	**49 (89)**	**40 (76)**	**–31 to 11**
Cardiovascular drugs	32 (42%)	79 (38%)	–17 to 8%	246 (497)	256 (481)	–118 to 138
Aspirin	15 (20%)	42 (20%)	–10 to 11%	55 (121)	62 (145)	–30 to 44
Indigestion drugs	10 (13%)	32 (15%)	–7 to 11%	18 (74)	16 (51)	–17 to 14
Respiratory drugs	7 (9%)	33 (16%)	–2 to 15%	75 (483)	43 (157)	–107 to 42

NA, not applicable.

medications' had less than 90 days' supply and very few had more than 270 days' supply over a year.

There were no statistically significant differences between the two groups in the pattern of prescribing for rescue medication or medications use for possible adverse events. The difference in cardiovascular prescribing approaches statistical significance. This difference is present at each follow-up time-point, which suggests that this difference is due to baseline differences rather than effect of the study medications.

PPS

NSAIDs overall use

During the first year of follow-up, 88% of those in the oral group received a prescription for an oral NSAID and none had a prescription for a topical NSAID. In the topical group, 81% had a prescription for a topical NSAID and 26% had a prescription for an oral NSAID. In the topical

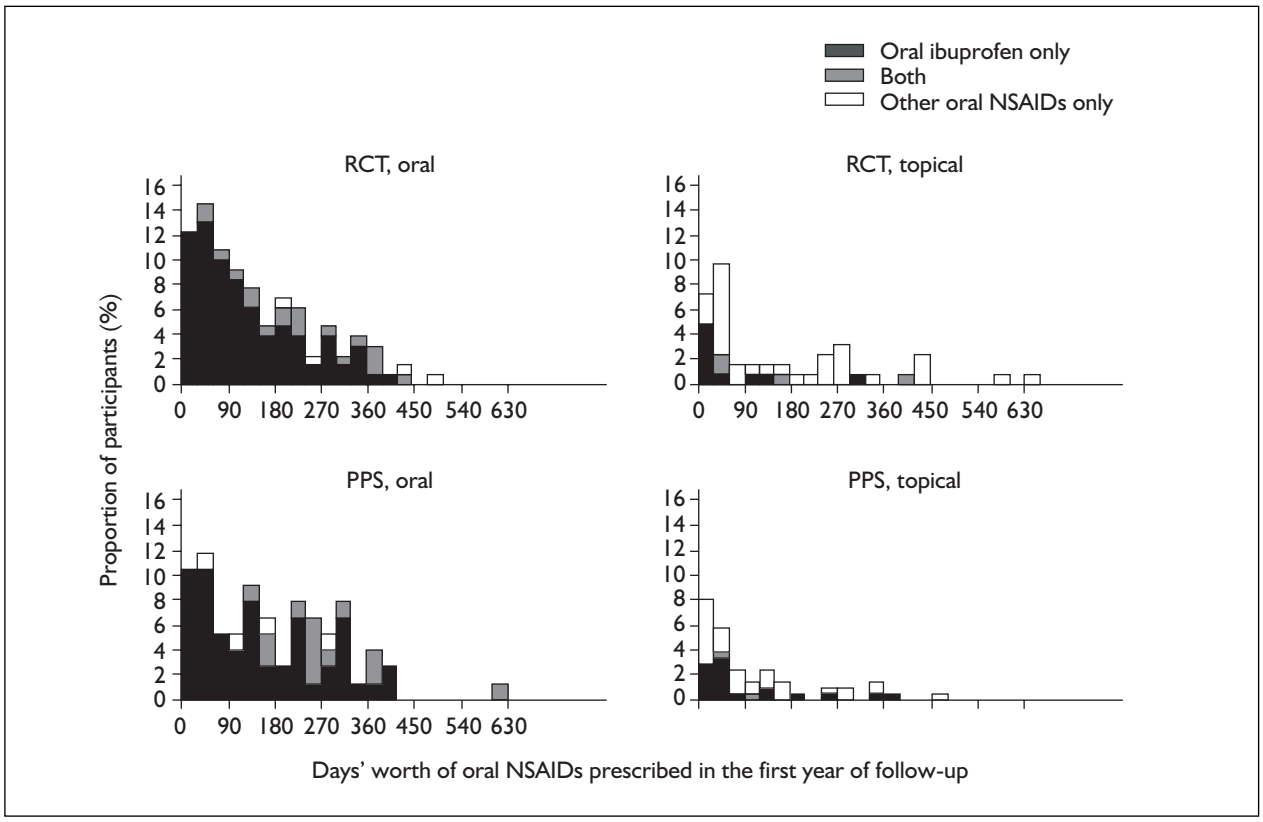


FIGURE 19 *Days' worth of oral NSAIDs prescribed over 12 months*

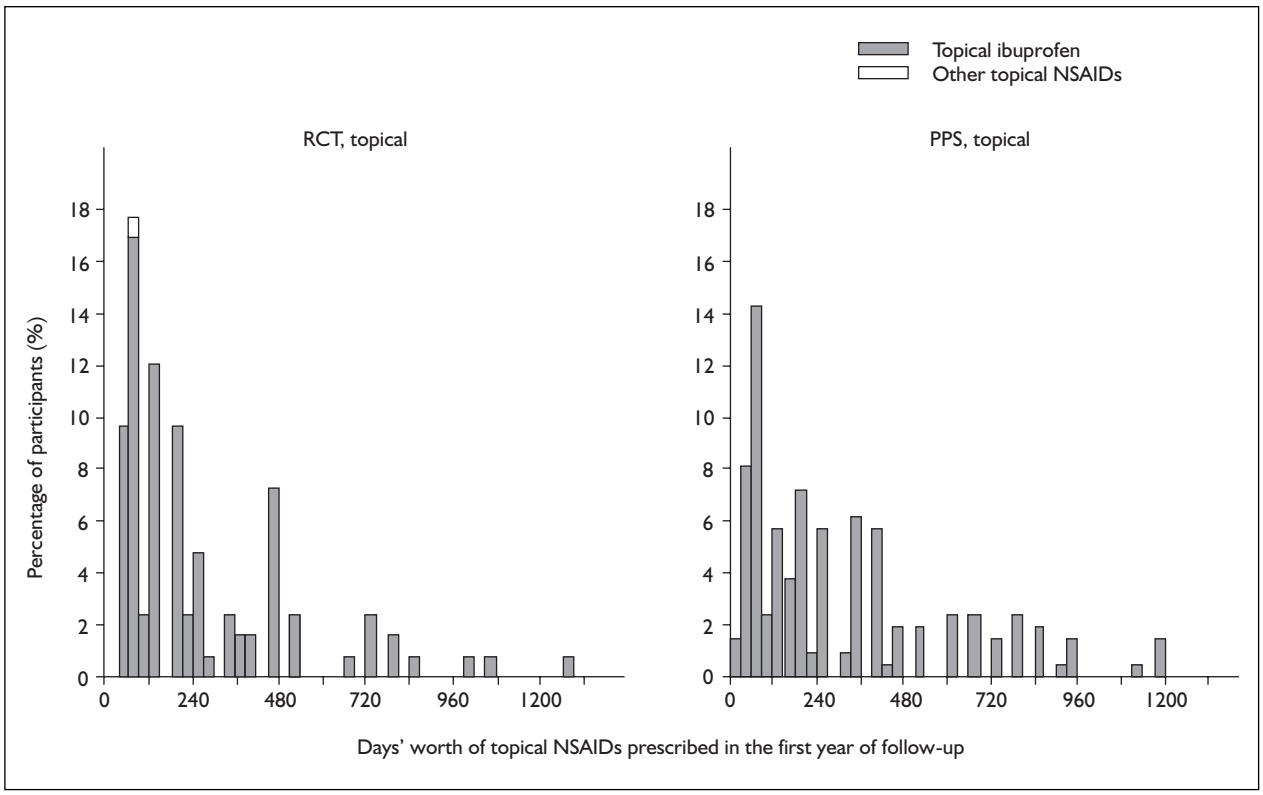


FIGURE 20 *Days' worth of topical NSAIDs prescribed over 12 months for topical groups in RCT and PPS. Data for use of topical preparations prescribed for participants in oral groups are not presented because of small numbers of prescriptions.*

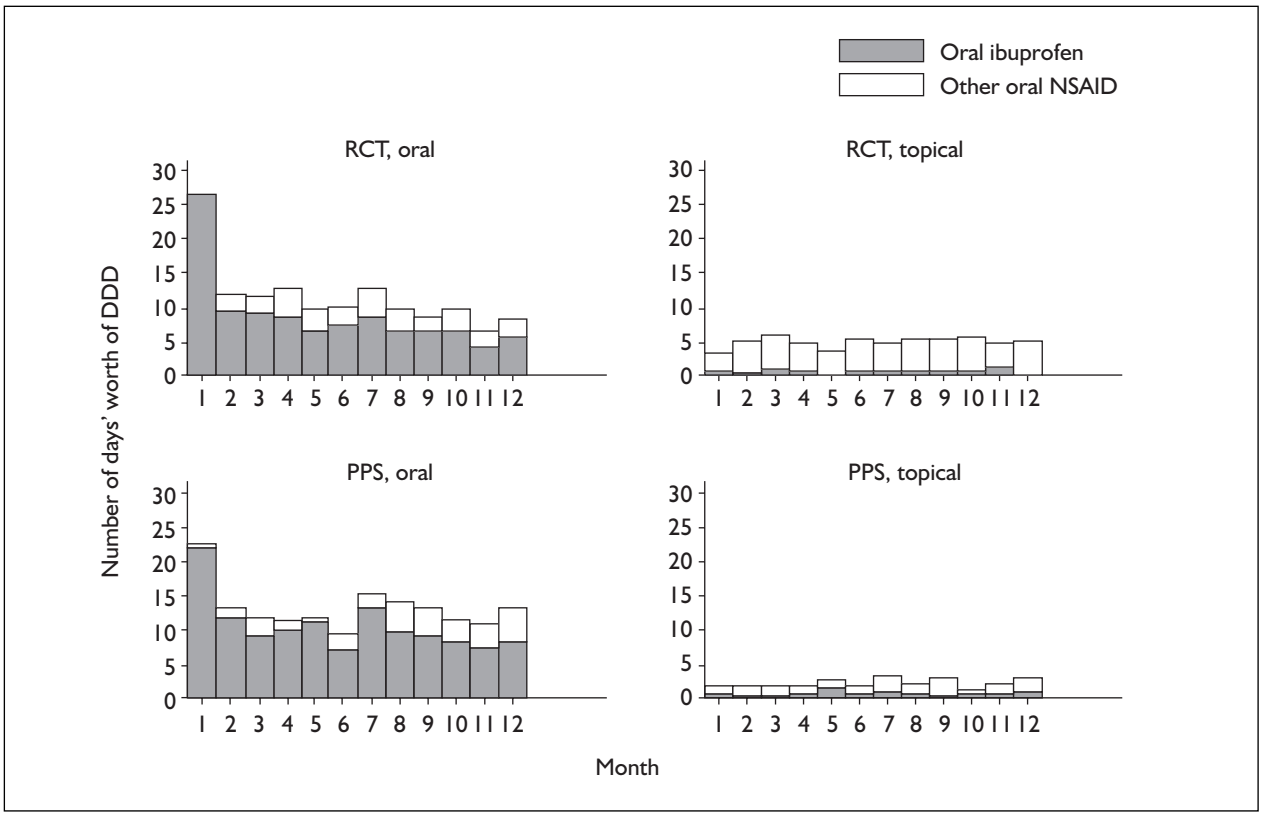


FIGURE 21 *Mean number of DDDs of oral NSAIDs prescribed by month for all participants*

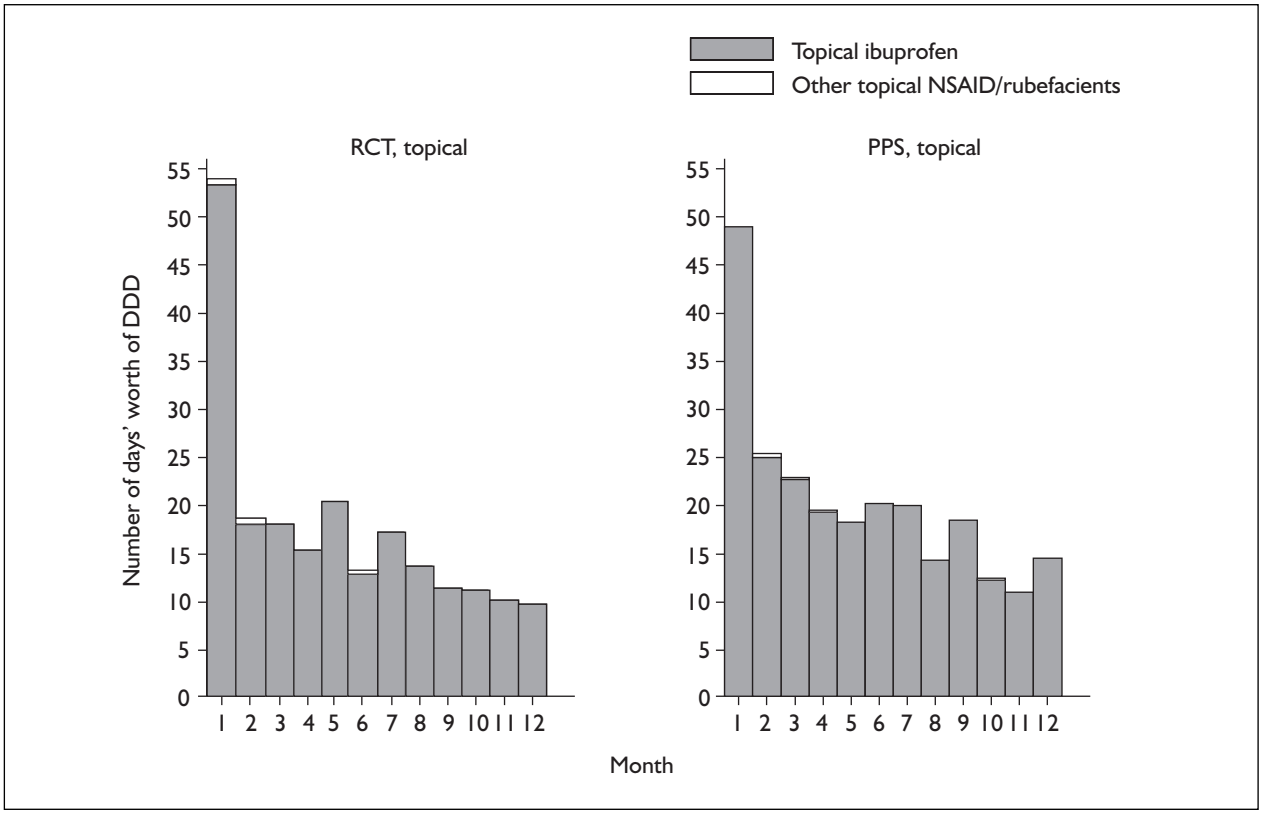


FIGURE 22 *Mean number of DDDs of topical NSAIDs and rubefacients prescribed by month for all participants for topical groups in RCT and PPS*

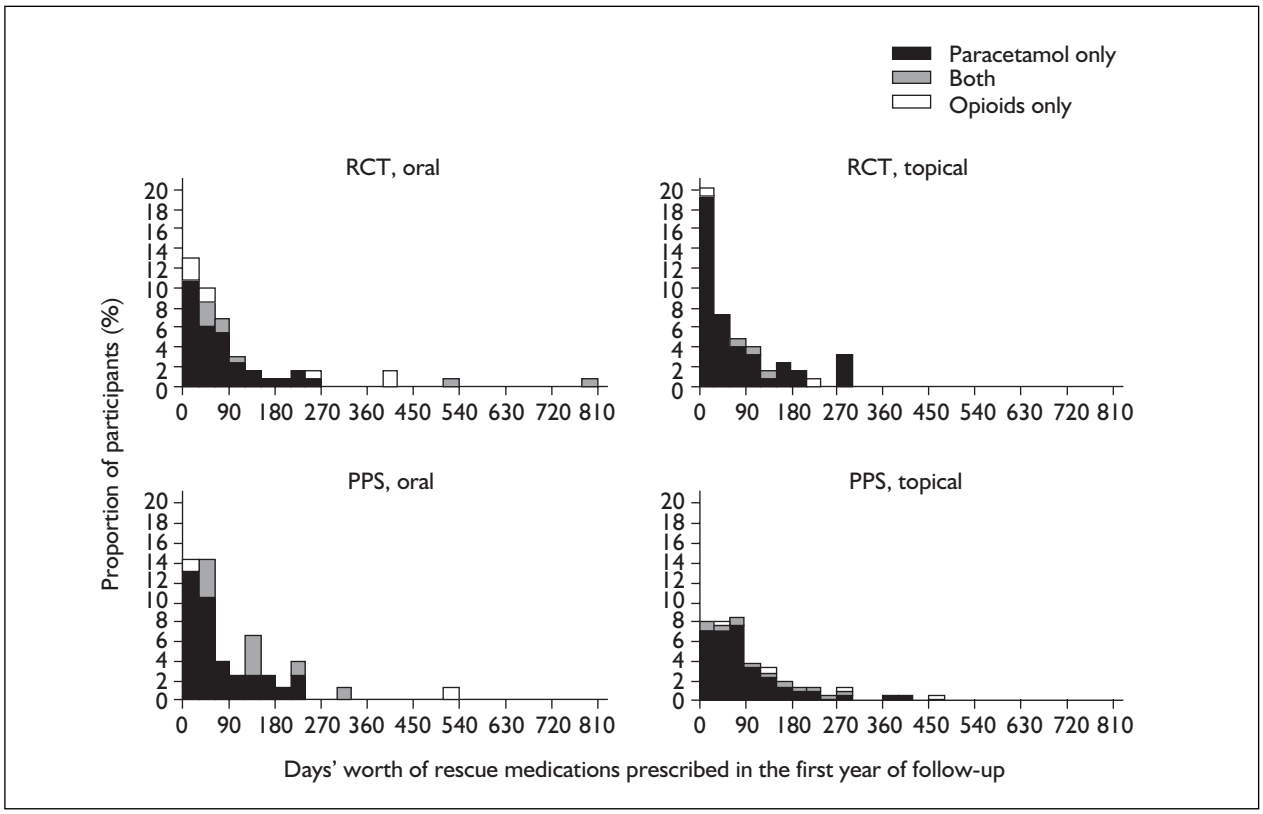


FIGURE 23 *Total DDDs of rescue medications prescribed over 12-month follow-up*

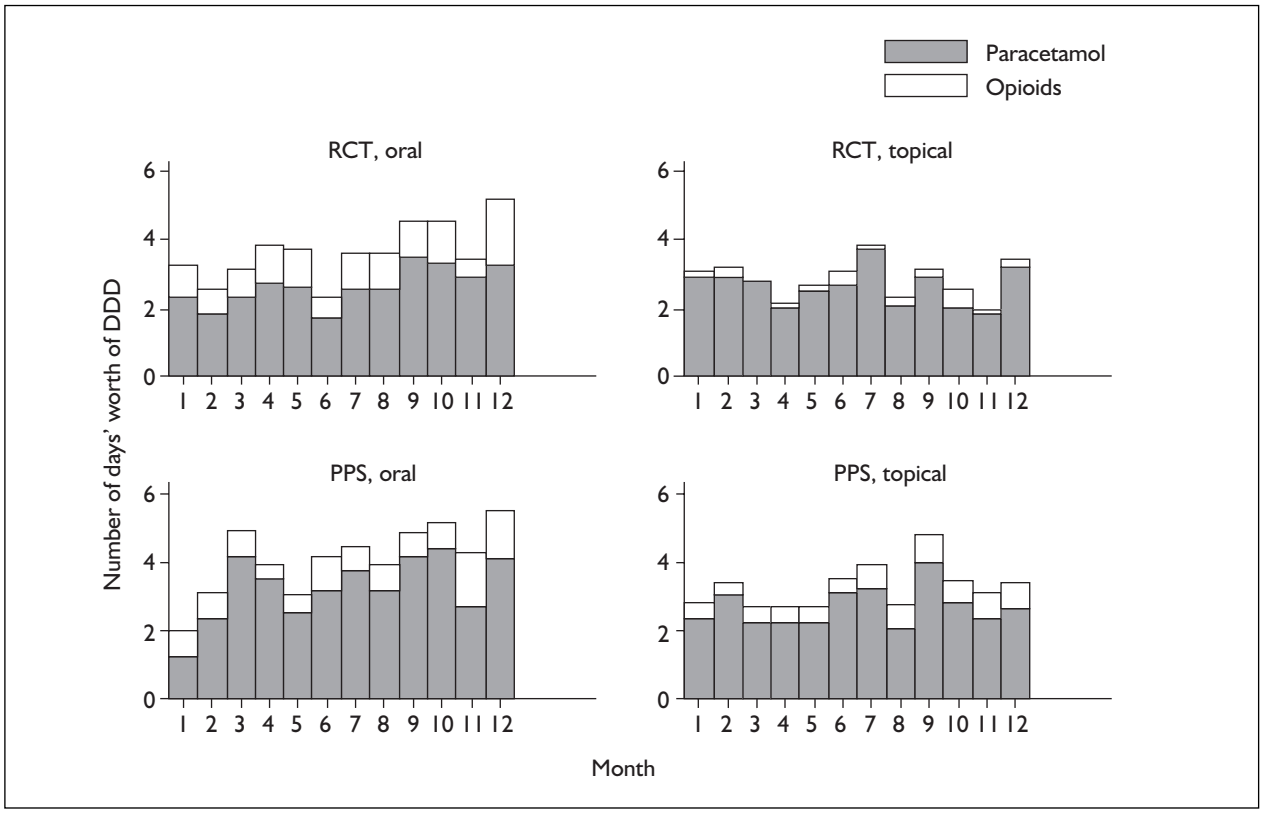


FIGURE 24 *Mean number of DDS of rescue medications prescribed by month for all participants*

group, fewer people had a prescription for oral ibuprofen (11%) than for another NSAID (17%). In contrast to the RCT, the proportion of those in the oral group who were prescribed an oral NSAID only fell from 75 to 62% between quarters one and four. No-one in the PPS oral group was prescribed a topical NSAID, possibly reflecting the stronger views of the minority who chose oral NSAIDs in the PPS (*Table 64–68*).

NSAID adherence

More of the oral group than the topical group were adherent to the route of administration. There was no significant difference in the proportions adherent, at 12 months, to their original prescriptions of oral or topical ibuprofen: 38% oral versus 31% topical. The greater adherence to ibuprofen and oral NSAIDs in the oral group probably reflects the fact that these people are more likely to have had good experiences of oral ibuprofen or NSAIDs prior to the start of the study; otherwise, they might have chosen the RCT or the oral PPS. These data show that overall adherence over 12 months of follow-up is by our definition excellent: 82% in the oral groups, not much worse in the topical groups (72–78%) and only slightly worse in the topical RCT than topical PPS.

Other drugs

More participants in the oral group than the topical group were prescribed 'rescue medication'; difference = 14%: (95% CI –26 to 0.4%). Importantly, as in the RCT, there was no difference in the average number of DDDs of 'rescue medication' (paracetamol and opioids) used (oral 49 DDDs versus topical 40 DDDs). Although not statistically significant, it is noteworthy that the trends are for there to be an excess of 'rescue medication' prescribing in the oral group. This means it is unlikely that the equivalence in pain-related outcomes is a consequence of participants supplementing ineffective topical preparations with other prescribed analgesics. Over the follow-up period, those in the oral group used progressively more 'rescue medication'. Since participants in the PPS oral group tended to have more severe or widespread pain at baseline, it would not be too surprising if they used more 'rescue medications'.

Adherence and WOMAC score

Participant-reported adherence with treatment route

The participant report of compliance with allocated treatment showed some differences between the oral and topical groups in the RCT. Those in the topical group reported using more of the alternative route of administration than those in the oral group: 16% versus 5% at 12 months [difference 11% (95% CI 4% to 18%)]. However, there was no difference in the overall proportion who reported that they had changed their treatments; this may include changes within routes of administration: 28% versus 32% [difference 4% (95% CI –6 to 15%)]. This apparent similarity masked two differences. First, fewer participants reported changing their oral preparation because of inadequate pain relief: 13% versus 23% [difference 11% (95% CI 2 to 20%)]; and second, more participants reported changing their oral medication because of adverse effects than those randomised to topical preparations: 11% versus 1% [difference –10% (95% CI –16 to –5%)] (*Table 67*).

Fewer participants in the PPS reported changing treatment when compared with the RCT, but a change of route of administration was still more likely in the topical group. In contrast to the RCT, there is no difference in the proportions reporting that they had changed treatment because of inadequate pain relief. In the PPS, twice as many people reported changing treatment because of adverse effect in the oral group when compared with the topical group (9% versus 4%). This was of borderline statistical significance ($p = 0.07$) (*Table 68*).

Participants were originally prescribed ibuprofen, either oral or topically, and it is likely that if either was ineffective or producing adverse events it would act as a trigger for changing treatment. Since few of the participants in the topical groups were prescribed oral ibuprofen, one would expect that their next choice of treatment, if ibuprofen was ineffective, would be a different oral NSAID. In the oral groups, using a different oral NSAID would be considered adherent, but this was not the case for the topical groups, so the comparison by adherence to any NSAID is likely to be biased. The following results are therefore presented by adherence to ibuprofen and route.

The pattern of adherence is similar in the four groups (*Table 69*), but there are substantial differences in outcome according to the participants' level of adherence. Looking at the whole data set we can see that, compared with those who were adherent and taking painkillers, those taking no painkillers have less pain: difference in WOMAC global score = –6.6, (95% CI –11 to –2.1), $p = 0.004$; and those who

TABLE 67 *The first participant-reported change of treatment, RCT*

RCT	Oral	Topical	Difference topical – oral (95% CI)
Total patients completed questionnaires at each time-point (not necessarily compliant)			
Baseline	144 (100%)	138 (100%)	
3 months	134 (93%)	130 (94%)	
6 months	129 (90%)	122 (88%)	
12 months	125 (87%)	122 (88%)	
Proportion taking other mode of NSAID for more days in past month			
3 months	4 (3%)	12 (9%)	
6 months	4 (3%)	23 (17%)	
12 months	7 (5%)	22 (16%)	11% (4 to 18%), $p = 0.002$
Patient-reported changed treatment			
0–3 months	18 (13%)	25 (18%)	
3–6 months	11 (7%)	10 (7%)	
6–12 months	12 (8%)	9 (7%)	
Subtotal	*41 (28%)*	*44 (32%)*	4% (–6 to 15%), $p = 0.53$
Changed treatment because inadequate pain relief			
0–3 months	9 (6%)	16 (12%)	
3–6 months	2 (1%)	11 (8%)	
6–12 months	7 (5%)	5 (4%)	
Subtotal	18 (13%)	32 (23%)	11% (2 to 20%), $p = 0.009$
Changed treatment because of any adverse effects[a]			
0–3 months	5 (3%)	1 (1%)	
3–6 months	7 (5%)	0 (0%)	
6–12 months	4 (3%)	0 (0%)	
Subtotal	*16 (11%)*	*1 (1%)*	–10% (–16 to –5%), $p < 0.001$
Changed treatment for other reasons (including pain elsewhere, doctor's advice or no information)			
3 months	4 (3%)	7 (5%)	
6 months	3 (2%)	0 (0%)	
12 months	2 (1%)	4 (3%)	
Subtotal	*9 (6%)*	*11 (8%)*	–2% (–8 to 4%), $p = 0.57$

[a] These are participant self-reports of adverse effects; they do not relate to the defined minor adverse effects reported elsewhere in this report.

were not adherent have more pain: difference in WOMAC global score = 8.1 (95% CI 2.7 to 13.5), $p = 0.004$.

The strongest predictor of follow-up WOMAC scores was the baseline WOMAC score (correlation coefficient 0.67, $p < 0.001$). Adjusting for this in a regression model, the effect on outcome of non-adherence to ibuprofen is not statistically significant. However, having been prescribed painkillers in the previous 3 months remains statistically significant, with an effect on the WOMAC global score at 12 months of –5 (95% CI –8 to –2), $p = 0.001$.

A regression analysis was carried out of the 12-month WOMAC global score adjusting for a common baseline effect over the four groups in order to investigate the effect of using or not using oral NSAIDs, topical NSAIDs, strong opioids, weak opioids and paracetamol-based drugs. The 12-month global WOMAC score was slightly higher in those taking oral NSAIDs and those taking strong opioids, but neither difference was statistically significant (*Table 70*). However, the use of any oral NSAID other than ibuprofen in the topical groups was associated with an increase of 7.7 (95% CI 1.8 to 13.6) points in the WOMAC global score ($p = 0.011$), and the use of paracetamol was associated with an increase in the WOMAC score of 6.5 (95% CI 3.0 to 10.1), $p < 0.001$. This effect was not seen in the oral groups. An interpretation was made that the participants in the topical groups who changed medication had a higher symptom threshold for change from their chosen/allocated treatment than

TABLE 68 *The first participant-reported change of treatment, PPS*

PPS	Oral	Topical	Difference topical – oral (95% CI)
Total patients completed questionnaires at each time-point (not necessarily compliant)			
Baseline	79 (100%)	224 (100%)	
3 months	74 (94%)	206 (92%)	
6 months	69 (87%)	200 (89%)	
12 months	72 (91%)	191 (85%)	
Proportion taking other mode of NSAID for more days in past month			
3 months	0 (0%)	14 (6%)	
6 months	3 (4%)	16 (7%)	
12 months	1 (1%)	23 (10%)	9% (4 to 14%), $p = 0.011$
Patient-reported changed treatment			
0–3 months	9 (11%)	27 (12%)	
3–6 months	5 (6%)	11 (5%)	
6–12 months	9 (11%)	7 (3%)	
Subtotal	*23 (29%)*	*45 (20%)*	–9% (–20 to 2%), $p = 0.098$
Changed treatment because inadequate pain relief			
0–3 months	4 (5%)	6 (3%)	
3–6 months	2 (3%)	9 (4%)	
6–12 months	4 (5%)	7 (3%)	
Subtotal	*10 (13%)*	*22 (10%)*	–3% (–11 to 5%), $p = 0.48$
Changed treatment because of any adverse effects[a]			
0–3 months	4 (5%)	7 (3%)	
3–6 months	1 (1%)	1 (0.4%)	
6–12 months	2 (2%)	0 (0%)	
Subtotal	*7 (9%)*	*8 (4%)*	–5% (–12 to 1%), $p = 0.072$
Changed treatment for other reasons (including pain elsewhere, doctor's advice or no information)			
3 months	1 (1%)	12 (5%)	
6 months	2 (3%)	2 (1%)	
12 months	3 (4%)	2 (1%)	
Subtotal	*6 (8%)*	*16 (7%)*	–0.5% (–7 to 6%), $p = 0.89$

[a] These are participant self-reports of adverse effects; they do not relate to the defined minor adverse effects reported elsewhere in this report.

those in the oral groups. The effect was slightly stronger in the RCT.

Adherence and adverse effects

No association was found between having had one of our defined gastrointestinal or renovascular adverse effects by 12 months and adherence in the 3 months prior to the 12-month questionnaire. However, an association was found between having had any respiratory adverse effects by 12 months and being non-adherent; the non-adherent participants were more likely to have had a respiratory adverse effect [odds ratio (OR) = 2.02 (95% CI 1.22 to 3.34), $p = 0.006$], and those in the RCT topical group were less likely to have had a respiratory adverse effects [OR = 0.42 (95% CI 0.21 to 0.85), $p = 0.015$] (each adjusted for the other).

Being in the topical group in the PPS did not affect the number of adverse effects. Since some of the adverse effects will have been identified some time before the 12-month follow-up and adherence was measured in the fourth quarter, it is possible that the apparent protective effect of being adherent is associated with participants changing treatment because of adverse effects.

Effect of prescribing on adverse effects

In this analysis, we have assumed that, after allowing for baseline differences, the effect of prescribing on adverse effects will be similar in all four groups. This was looked at in two ways: first using all participants and second using data only from participants in the RCT. The latter method excludes data from the PPS

TABLE 69 *Adherence to treatment in 12 months, RCT*

	RCT, oral *n* = 130	RCT, topical *n* = 124	PPS, oral *n* = 76	PPS, topical *n* = 210	Total *n* = 540
Adherent to NSAID and route – prescribed some drugs					
1st quarter[a]	103 (79%)	92 (74%)	53 (70%)	147 (70%)	395 (73%)
2nd quarter	70 (54%)	51 (41%)	43 (57%)	95 (45%)	259 (48%)
3rd quarter	62 (48%)	38 (31%)	42 (55%)	88 (42%)	230 (43%)
4th quarter	49 (38%)	33 (27%)	39 (51%)	66 (31%)	187 (35%)
Adherent to NSAID and route – prescribed no painkilling drugs (except paracetamol)[b]					
1st quarter	17 (13%)	16 (13%)	17 (22%)	45 (21%)	95 (18%)
2nd quarter	47 (36%)	45 (36%)	25 (33%)	78 (37%)	195 (36%)
3rd quarter	51 (39%)	48 (39%)	26 (34%)	80 (38%)	205 (38%)
4th quarter	57 (44%)	56 (45%)	23 (30%)	94 (45%)	230 (43%)
Not adherent to NSAID and route					
1st quarter	10 (8%)	16 (13%)	6 (8%)	18 (9%)	50 (9%)
2nd quarter	13 (10%)	28 (23%)	8 (11%)	37 (18%)	86 (16%)
3rd quarter	17 (13%)	38 (31%)	8 (11%)	42 (20%)	105 (19%)
4th quarter	24 (18%)	35 (28%)	14 (18%)	50 (24%)	123 (23%)
Adherent to ibuprofen and route – prescribed some painkilling drugs					
1st quarter	96 (74%)	92 (74%)	49 (64%)	147 (70%)	384 (71%)
2nd quarter	54 (42%)	51 (41%)	40 (53%)	95 (45%)	240 (44%)
3rd quarter	48 (37%)	38 (31%)	33 (43%)	88 (42%)	207 (38%)
4th quarter	38 (29%)	33 (26%)	29 (38%)	66 (31%)	166 (31%)

[a] Slight underestimate of non-adherence as the initial days' worth of treatment, 8 for oral and 24 for topical, are not counted.
[b] This category comprises all the patients who are not prescribed any painkilling drugs, other than paracetamol, during the appropriate period.

TABLE 70 *WOMAC scores at 12 months by adherence to ibuprofen and route*

	Mean (SD)			
	RCT, oral *n* = 115	RCT, topical *n* = 111	PPS, oral *n* = 67	PPS, Topical *n* = 178
No painkillers (except paracetamol)	32 (21)	35 (21)	33 (20)	35 (23)
Adherent to ibuprofen and route (taking pain killers)	37 (21)	38 (21)	40 (21)	45 (23)
Not adherent and taking painkillers	44 (23)	47 (23)	50 (18)	49 (23)
p-Value from ANOVA	0.052	0.057	0.039	0.005
Mean overall	36 (22)	39 (22)	41 (21)	42 (24)

ANOVA, analysis of variance.

topical group whose baseline characteristics are different from the other groups. Both datasets were analysed in two ways: using a binary category of 'any prescription versus no prescription' and considering the effect for each additional 30 days' worth of treatment prescribed in different drug groups in the 3 months prior to the outcome measurement.

The only adverse effect measure that appeared to have been affected by drug use was Hb. The results for any topical NSAID versus none were 0.16 (95% CI 0.01 to 0.31) for the whole group and 0.20 (95% CI –0.04 to 0.44) for the RCT. The effect of 30 days' worth of topical NSAID treatment was to increase Hb by 0.04 g/l (95% CI 0.01 to 0.07), $p = 0.019$, in the whole dataset and

by 0.06 g/l (95% CI 0.01 to 0.12), $p = 0.03$, in the RCT. This is a biologically plausible observation: if those using topical NSAIDs use fewer oral NSAIDs then one might expect less gastrointestinal blood loss. The absolute differences in Hb were small (0.16 g/dl) and unlikely to be important for an individual patient. However, these mean differences may conceal some participants with more substantial falls in Hb. There was no significant drug effect on levels of $\log_e$ (ferritin) creatinine, diastolic or systolic blood pressure, FEV_1 or PEF.

Risk–benefit analysis of WOMAC and adverse effect data

A risk–benefit analysis allowed us to estimate the trade-off between adverse events and pain reduction. The strongest predictor of the WOMAC score at 12 months was the WOMAC score at baseline. Also, severity of pain at baseline is likely to have affected NSAID consumption and thus had an effect on adverse events. Hence we might expect both baseline and 12-month WOMAC scores to be associated with any adverse effects that have arisen during the follow-up period or been identified at the 12-month assessment. We investigated the relationship between our defined adverse effects over 12 months and the WOMAC scores at these two time-points both graphically and using logistic regression. The relationship between 12-month WOMAC score not adjusted for its baseline and outcome measures adjusted for their baseline is reported. For completeness, further information is given on these results when adjusted for baseline WOMAC.

Figures 25–28 show 12-month and baseline global WOMAC scores for those with and without one of our defined adverse effects by the 12-month follow-up in the RCT. The graphs on the right are of those with an adverse effect and those on the left are of those without an adverse effect. The graphs of those with adverse effects show a similar pattern in the relationship between baseline and 12-month WOMAC scores. However, in several of the figures it appears that those with adverse effects are more likely to have higher baseline and 12-month scores, that is, to be worse off than those with no adverse effects.

Using logistic regression, we found that the strongest predictor of having one of our defined adverse effects was the baseline WOMAC global score and there was no independent effect of WOMAC global score at 12 months for any adverse effects after adjustment for baseline WOMAC score. There were no non-linear associations.

In a second model, the effect was estimated of a 10-point difference in the WOMAC global score at 12 months within each of our four groups. We also included baseline measures of the outcome, age, sex and having an occupational code of 1, 2 or 3. Groups were combined if there was no significant difference between the effects within pairs of the groups. Age, sex, higher occupational code and the baseline measure were kept in the models whether or not they were statistically significant. The effects of a change in 10 points in the WOMAC score on the measured outcomes are shown in *Table 71* and results for the RCT only are given in *Table 72*.

In the RCT, there was a consistent relationship in both groups where $\log_e$ (ferritin) and systolic blood pressure are raised and FEV_1 and PEF are lowered as the global WOMAC score increases. The effect on diastolic blood pressure was smaller and marginally significant when the effect was combined over both RCT groups. Changes in Hb and creatinine were not associated with WOMAC score at 12 months in either the RCT or the PPS.

The relationship between WOMAC scores and some outcomes was clearly different in the PPS topical group. Of those variables which had a significant association with WOMAC score in the RCT, only the effect of WOMAC score on changes in PEF was similar in both PPS groups. For ferritin and FEV_1, the results in the PPS oral group were similar to those seen in the RCT. However, there was not a relationship between ferritin and FEV_1 and WOMAC in the PPS oral group. This difference between the PPS oral and topical groups was statistically significant (ferritin $p < 0.001$, FEV_1 $p = 0.009$). The relationship between systolic blood pressure and the WOMAC score was smaller in the PPS oral group than in the RCT and smaller still in the topical group. The PPS topical group was different from the other three groups combined ($p = 0.040$) but not from the PPS oral group on its own.

Further adjusting the effects of WOMAC score at 12 months for baseline WOMAC score, i.e. investigating the relationship between adverse effects with change in WOMAC scores, gave statistically significant associations between the WOMAC score at 12 months with $\log_e$ (ferritin) and FEV_1 in the RCT. A 10-point increase in WOMAC at 12 months, adjusted for baseline, is associated with a percentage increase in ferritin levels of 5.8% (95% CI 1 to 10.5%), $p = 0.017$, and a decrease in FEV_1 values of –0.027 (95% CI –0.05 to 0.003), $p = 0.023$. For both of these result there

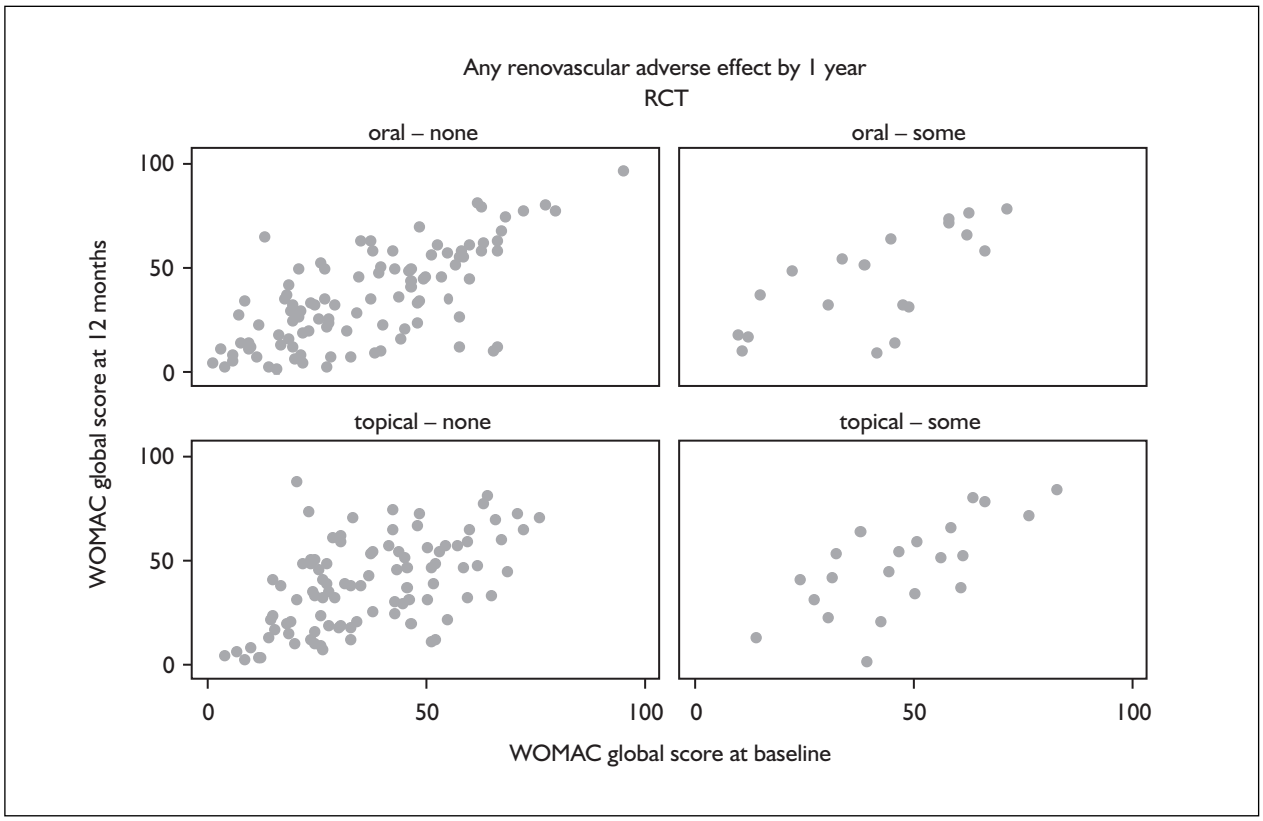


FIGURE 25 *Relationship between adverse renal effects and global WOMAC scores at baseline and 12 months for the RCT*

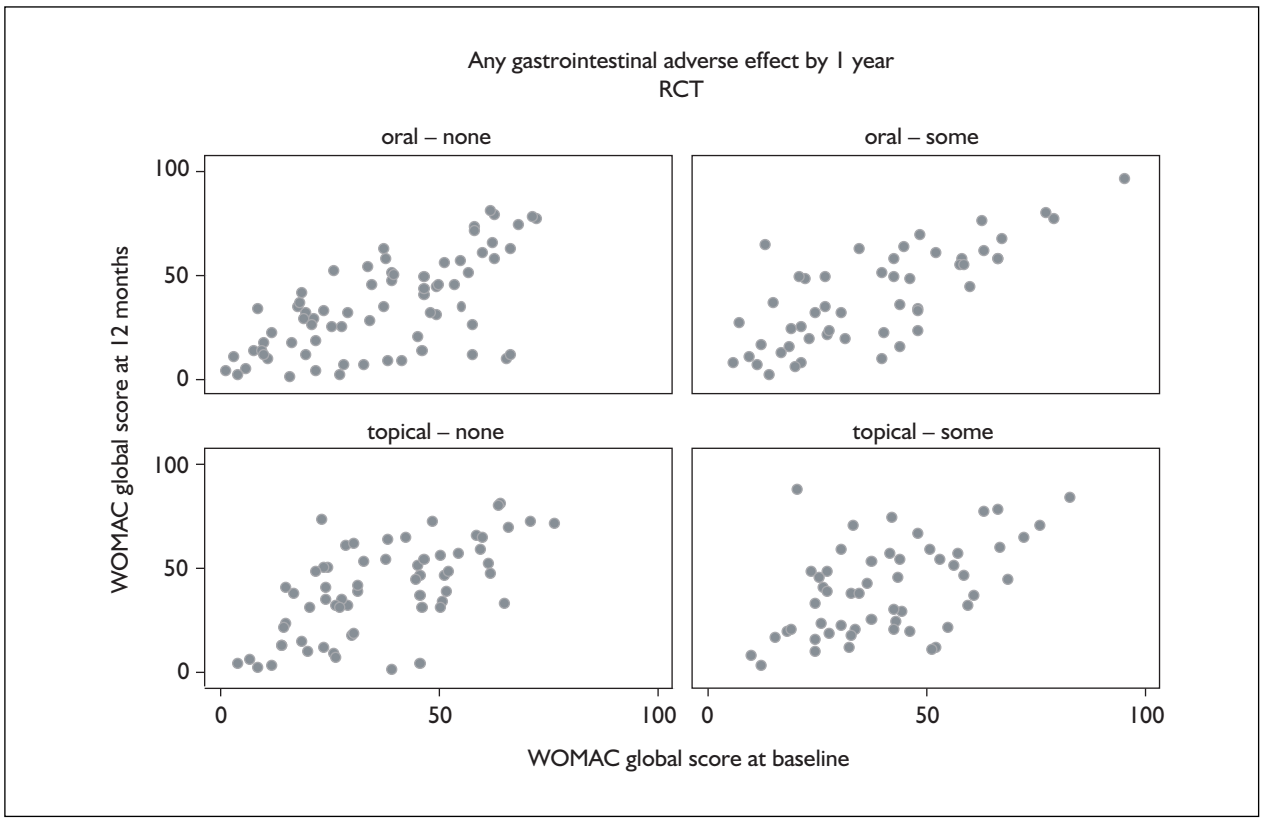


FIGURE 26 *Relationship between adverse gastric effects and global WOMAC scores at baseline and 12-months for the RCT*

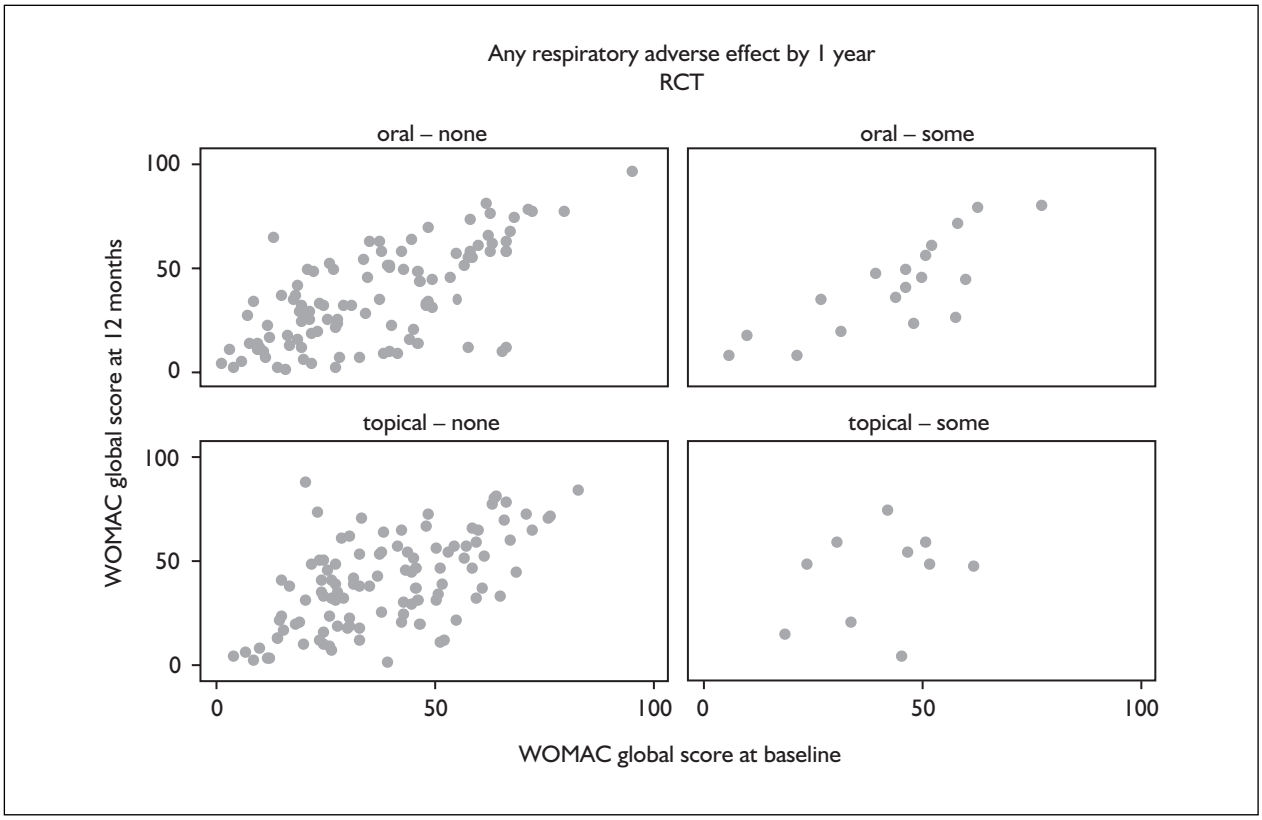


FIGURE 27 *Relationship between adverse respiratory effects and global WOMAC scores at baseline and 12-months for the RCT*

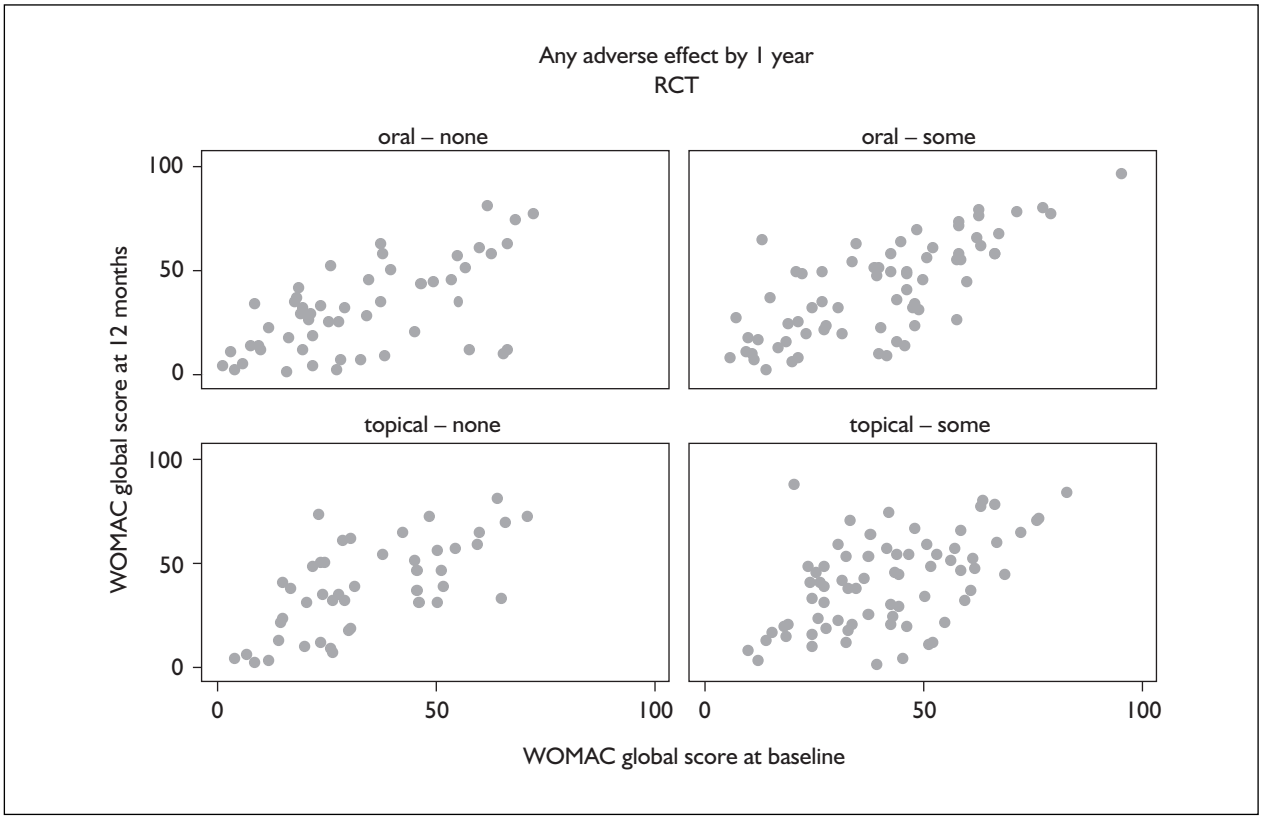


FIGURE 28 *Relationship between adverse effects and global WOMAC scores at baseline and 12-months for the RCT*

TABLE 71 *Mean difference (95% CI) in adverse event measures at 12 months, within groups, for each 10 mm increase in global WOMAC score at 12-months (results adjusted for age, sex, occupational code and baseline values of the outcome)*

	RCT, oral	RCT, topical	PPS, oral	PPS, topical
Hb	0.02 (–0.02 to 0.06) $p = 0.36$	0.01 (–0.03 to 0.05) $p = 0.68$	0.03 (–0.02 to 0.08) $p = 0.19$	0.02 (–0.02 to 0.05) $p = 0.33$
Log_e (ferritin)	0.031 (0.001 to 0.06) $p = 0.041$	0.045 (0.016 to 0.07) $p = 0.002$	0.044 (0.011 to 0.077) $p = 0.009$	–0.01 (–0.04 to 0.02) $p = 0.61$
Creatinine	–0.1 (–0.9 to 0.6) $p = 0.69$	0.1(–0.5 to 0.7) $p = 0.75$	–0.2 (–1.0 to 0.5) $p = 0.54$	–0.0 (–0.6 to 0.5) $p = 0.92$
Diastolic blood pressure	0.2 (–0.2 to 0.6) $p = 0.44$	0.2 (–0.1 to 0.6) $p = 0.21$	0.3 (–0.2 to 0.8) $p = 0.19$	0.2 (–0.1 to 0.6) $p = 0.17$
Systolic blood pressure	1.1 (0.3 to 1.9) $p = 0.003$)	1.2 (0.4 to 1.9) $p = 0.002$	0.8 (–0.1 to 1.7) $p = 0.080$	0.5 (–0.2 to 1.1) $p = 0.16$
FEV_1	–0.021 (–0.039 to –0.002) $p = 0.032$	–0.025 (–0.039 to –0.006) $p = 0.008$	–0.025 (–0.046 to –0.004) $p = 0.020$	0.01 (–0.008 to 0.029) $p = 0.26$
PEF	–4.1 (–7.4 to –0.8) $p = 0.015$	–2.7 (–5.9 to 0.5) $p = 0.093$	–4.6 (–8.4 to –0.8) $p = 0.018$	–2.7 (–5.4 to –0.01) $p = 0.050$

TABLE 72 *Mean difference (95% CI) in adverse event measures at 12 months, within groups, for each 10 mm increase in global WOMAC score at 12-months, RCT (results adjusted for age, sex, occupational code and baseline values of the outcome)*

	RCT, oral	RCT, topical	In all RCT, if significant and no interaction	Significant effects of group
Hb	0.007 (–0.04 to 0.05) $p = 0.73$	0.001 (–0.05 to 0.05) $p = 0.95$	NS	
Log_e (ferritin)	0.032 (–0.01 to 0.07) $p = 0.10$	0.044 (0.007 to 0.08) $p = 0.044$	0.038 (0.005 to 0.071) $p = 0.026$	
Creatinine	–0.2 (–0.9 to .6) $p = 0.68$	0.5 (–0.4 to 1.3) $p = 0.29$	NS	Topical –3.4 (–5.9 to –0.9) $p = 0.09$[a]
Diastolic blood pressure	0.3 (–0.2 to 0.8) $p = 0.18$	0.4 (–0.05 to 0.8) $p = 0.078$	0.4 (–0.04 to 0.8) $p = –0.081$	
Systolic blood pressure	1.1 (0.1 to 2.0) $p = 0.029$)	1.2 (0.3 to 2.1) $p = 0.010$	1.1 (0.3 to 2.0) $p = 0.007$	
FEV_1	–0.024 (–0.044 to –0.004) $p = 0.021$	–0.028 (–0.047 to –0.008) $p = 0.0.002$	–0.026 (–0.044 to –0.008) $p = 0.005$	
PEF	–4.8 (–8.7 to –0.9) $p = 0.015$	–3.3 (–7.1 to 0.5) $p = 0.086$	–4.0 (–7.4 to –0.6) $p = 0.021$	

NS, not significant.
[a] Univariate result.

are similar associations in the oral PPS group, whereas in the topical PPS group there is no association between adverse effects and change in the WOMAC score.

The analysis of adverse effects using logistic regression showed stronger effects of baseline WOMAC scores on all the outcomes, and only ferritin and FEV_1 can be shown to have been affected by the change in WOMAC scores over the year. Blood pressure and PEF are clearly associated with WOMAC scores but the relationship is either with the average WOMAC scores over the year or takes longer to manifest itself.

TABLE 73 *Planned admissions to end of follow-up*

	Oral		Topical	
	No. of admissions	**No. of participants**	**No. of admissions**	**No. of participants**
RCT		*n* = 144		*n* = 138
Knee surgery	10	10	10	8
Other orthopaedic	12	11	3	3
Abdominal and gynaecological disorders	9	9	9	7
Other	11	10	12	11
Total	42	38[a] (26%)	34	26[b] (20%)
PPS		*n* = 79		*n* = 224
Knee surgery	7	6	21	17
Other orthopaedic	8	7	14	11
Abdominal and gynaecological disorders	10	8	14	13
Other	5	5	14	13
Total	30	24[a] (30%)	63	47[ac] (21%)

[a] 2 participants were admitted in more than one category.
[b] 3 participants were admitted in more than one category.
[c] 7 participants were admitted in more than one category.

In summary, it was not possible to show any differences in the balance of risks and benefits in the RCT between the two groups. However, in the PPS there is a different pattern to the relationship between risks and benefits; a better WOMAC score is associated with a worse ferritin and a better FEV_1 in the PPS oral group, but not in the PPS topical group. Therefore, at least in those patients who express a preference for topical preparations, it may be less important to consider the trade-off between risk and benefits than when oral NSAIDS are preferred.

Other hospital admissions

Data on causes of hospital admissions were collected for the economic analysis and we present summary data on the reasons for hospital admissions here. These have been broken down into knee surgery, other orthopaedic admissions, admissions for abdominal and gynaecological disorders and other admissions. All admissions during the follow-up period have been included. No obvious differences were found in the total number of planned hospital admissions or planned hospital admissions in different categories in either the RCT or the PPS. Because individual participants could have had multiple admissions in different categories, the only meaningful statistical analysis was to compare the proportions with one or more planned hospital admission. This was not statistically significant in either study; in the RCT, topical minus oral was 8% (95% CI –2 to 17%) and in the PPS, topical minus oral was 9% (95% CI –1 to 21%). (*Table 73*).

During this coding exercise we were blind to treatment allocation, and we were surprised how many of our participants had had knee replacements, 25/573 (4%), particularly as planned knee replacement was an exclusion criterion. A *post hoc* analysis was carried out for differences in the proportions and rates of first knee replacements between oral and topical groups; no significant differences were found in these analyses (*Table 74*).

Finally, a separate analysis was performed taking the number of participants who had had a gastroscopy during the follow-up period. Mainly these were outpatient procedures, but some were undergone whilst the participant was an inpatient and have already been included in the planned abdominal and gynaecological admissions. All gastroscopies were used in this analysis. There were no significant differences between the groups in the number of gastroscopies performed (*Table 75*).

Summary of results

Changes in global WOMAC scores at 12 months in both the topical and oral groups were equivalent. In the RCT, there was a two-point difference in global WOMAC score (95% CI –2 to 6). In the preference study, there was a one-point difference (95% CI –4 to 6).

TABLE 74 *Knee replacements*

	Oral	Topical	Topical – oral (%)	Difference in rates per 100 person years (topical – oral) (95% CI)
RCT	*n* = 140	*n* = 136		
1st knee replacement	5 (4%)	4 (3%)	–0.6, *p* = 1	–0.4 (–3.0 to 2.2%)
2nd knee replacement	1 (1%)	0 (0%)	–	
PPS	*n* = 77	*n* = 220		
1st knee replacement	3 (4%)	13 (6%)	1.1, *p* = 1	2.0 (–3.3 to 7.3%)
2nd knee replacement	0 (0%)	0 (0%)	0	

TABLE 75 *Gastroscopies performed*[a]

	Oral	Topical	Risk difference (%)	Difference in rates per 100 person years (95% CI)
RCT	*n* = 140	*n* = 137		
Gastroscopies	5 (4%)	2 (1%)	–2.1, *p* = 0.45	–1.1 (–3.1 to 0.9)
PPS	*n* = 78	*n* = 220		
Gastroscopies	1 (1%)	6 (3%)	1.4, *p* = 0.68	0.7 (–0.9 to 2.2)

[a] Topical – oral (negative values favour topical). Only first gastroscopy for any participant is counted.

There were no differences in rates of major adverse effects in the RCT or preference study. In the RCT, the oral group had more minor adverse effects: more had respiratory adverse effects: 17% versus 10% (95% CI –17 to –2.0%); the change in serum creatinine was 3.7 mmol/l less favourable (95% CI 0.9 to 6.5); and more participants changed treatment because of adverse effects (11% versus 1%) (95% CI for difference –16 to –5%). Minor adverse events rates were similar in the two preference study groups. In the RCT, the topical group had a higher 3-month chronic pain grade score, and more participants changed treatment because of ineffectiveness.

Chapter 5

Economic evaluation of oral and topical ibuprofen

Introduction

The aim was to compare the costs and benefits of advice to use preferentially topical or oral ibuprofen, from both a NHS and Personal and Social Services (PSS) (henceforth NHS) perspective. An assessment was made of the cost–utility of topical compared with oral preparations in individuals with chronic knee pain, using healthcare services utilisation and health outcomes data collected during the trial.

Methods

Total costs and health outcomes

The total cost of care for each arm of the trial was calculated and expressed in UK sterling pounds. Health outcomes were calculated using utilities weights based on quality of life data collected using the EQ-5D data during the study. These are expressed in quality-adjusted life-years (QALYs).

Cost–utility

An incremental cost-effectiveness ratio (ICER) was calculated.[122] This is the ratio of the difference in total cost of care between advice to use preferentially topical and oral medication, compared with the total difference in QALYs between the two interventions. The ICER provides the relative 'cost' of one additional QALY for any individual with knee pain. The variability in the ICER in relation to randomness was assessed using the joint incremental costs and QALYs calculated from random samples extracted from the original study data.[123] Since the cost-effectiveness of a treatment depends on the policy maker's willingness to pay for one QALY, we assessed the cost-effectiveness of advice to use topical ibuprofen for a range of values of the willingness from £0 to £40,000.

Cost–utility was assessed from both an NHS perspective and a social perspective. The NHS perspective included all costs supported by the NHS and PSS. The social perspective was broader and included the cost of privately purchased goods and services related to knee pain, and costs of domiciliary help or other care, some of which may be provided informally by the patient's carer.

Separate analyses were carried out for the RCT and the PPS to assess whether individuals' preferences for treatment had an effect on the cost-effectiveness of these treatments. For both studies, an assessment was made of the cost–utility for two distinct time horizons of 12 and 24 months. Not all participants in the RCT had 24 months of follow-up; therefore, for the 24-month horizon all the follow-up data available before the end of the study were used. For the 24-month horizon, total costs and health outcomes were discounted, using a discount rate of 3.5%, according to Treasury Guidelines.[124]

Data collection

Resource utilisation data

Data were collected on the use of healthcare from participants' general practice records. Data collected included drug prescriptions, type and number of consultations in primary care, type and number of referrals to secondary care outpatient services, type and quantity of diagnostic tests, physiotherapy services, admissions for procedures, accident and emergency (A&E) episodes and planned or unplanned hospital admissions.

Hospital admissions were first identified from patient questionnaires and an initial search of participant's general practice records. Copies were then obtained of all hospital discharge letters relating to these admissions. Two study team members, both GPs, working independently (PC and MU), coded these for cause of admission using Healthcare Resource Groups (http://www.ic.nhs.uk/casemix/hrg/hrg1, accessed 4 December 2006) and recorded the duration of the admission: they were blind to the study group. They conferred to resolve any disagreements. Any remaining disagreements would have been arbitrated by a third member of the team. We only coded admissions for which a hospital discharge slip or letter was available, or from other letters that indicated that an admission had taken place during the study period. Data were collected about equipment or other aids directly from study participants via the follow-up questionnaires. They were asked to indicate which items were either provided by the NHS or purchased directly. In addition, participants reported non-NHS consultations they had had.

In the base case, costs were included if they were related to knee pain, treatment or adverse effects of treatment. The identification of relevant costs can be difficult; however, there were a few major health costs that could not plausibly be related to knee pain or NSAID use. These included admissions for cancer-related events and other causes of admissions such as hernia repairs, whooping cough, skin, facial and nose procedures and hearing aid implantation.

Prescription data for NSAIDs were broken down into ibuprofen and others. In the base case, we included the cost of drugs groups whose prescribing rate was most likely to be affected by treatment group, namely paracetamol, aspirin, mild and strong opioids, cardiovascular drugs, indigestion remedies and respiratory drugs.

Data on consumption of diagnostic tests, such as X-rays and gastroscopies, were collected using a separate collection form. All blood tests were included in the economic analysis, as it was not possible to decide which were not potentially related to NSAID use.

A sensitivity analysis was conducted including all healthcare costs, to assess the robustness of the limitation of costs included in the base case.

All healthcare use, except for initial starter packs, was participant initiated. For this reason, no attempt was made to exclude protocol-driven resource consumption and costs. Exceptions were blood tests and visits conducted in relation to recruitment to, and follow-up within, the trial, which were excluded from the cost of care.

Unit costs

Unit costs for the UK were obtained from published sources. Unit costs for the year 2006 were used, actualising unit costs for inflation using the Healthcare Price Index[125] when necessary.

Prescription costs

Details were obtained for all prescriptions issued during the study period from participants' general practices. Unit costs for prescribed items were obtained from the Prescription Cost Analysis database for 2005 (http://www.ic.nhs.uk/pubs/prescostanalysis2005, accessed 4 December 2006). Total prescription costs were then calculated using the average cost per dose for each product obtained from the database and the total quantity of each product prescribed; where appropriate broken down by drug group.

Consultation costs

Consultations in general practice were costed using GP and nurse visits costs from published UK sources.[125] These were £25 for GP surgery visits, £71 for GP home visits and £11 and £18 for nurse visits in the surgery or at home, respectively (actualised). Unit costs were inclusive of ancillary staff costs, overheads and training costs.

Costs were obtained for services delivered in primary care, such as counselling or social services assessment; unit costs were from the same source.[125] Unit costs were obtained for consultant, physiotherapy and rehabilitation outpatient consultations (*Table 97*, Appendix 3) from the NHS Reference Costs Database for 2005.[126]

Diagnostic testing costs

Unit costs were obtained for diagnostic tests from published primary costing studies conducted in the UK[127] or other literature.[128]

Hospital admission costs

Unit costs for hospital admissions and A&E attendances were obtained from the NHS Reference Cost Database for 2005, which contains published costs for all Hospital Trusts in England and Wales.[126] Reference costs are calculated using a top–down allocation method, and include staff costs, consumables and procedure costs (*Table 98*, Appendix 3).

Equipment and aids costs

Data were collected on the type and quantity of equipment and aids used from participants during follow-up, alongside the collection of effectiveness data, using postal questionnaires. Data included publicly provided or privately purchased equipment and the prices paid for privately purchased items. These quantities were used to calculate costs (*Table 76*). Since the majority of items dispensed by the NHS were also available for private purchase, items provided by the NHS were valued using market rather than NHS acquisition costs. Data on the NHS costs of providing these items are not easily available. The likely differences between the market purchase price and NHS costs, including a discount, would be small for most items, since most items were relatively low in cost. Therefore, it was assumed that the discounts obtained by the public sector for the majority of items were negligible, and equally distributed in the oral and topical groups.

Patients and family care costs

Data were collected on the cost of domiciliary help or other care purchased by families and hours of

TABLE 76 *Unit costs, equipment and aids*

	Type	Cost per item (average) (£)
Mobility aids	Walking stick or frame	13
	Wheelchair	33
	Wheel shop rider; mobility scooter; three-wheel tricycle	1287
Home adaptations or furniture	Bannister, walking rails	37
	Bathing or shower seat, bath lift (non-electric)	9
	Easy chair, kitchen chair	314
	Bath lift, electric	1399
	Stair lift, electric	1347
	Bed and other similar adaptations	249
Personal or disposable aids	Elasticised knee or ankle support or bandages, knee or leg braces	18
	Thermal knee support	57
Other	Other (exercise aids; magnopulse; pain(r)gone pen; gripper; helping hand)	44

informal care in the follow-up questionnaires. Hourly costs of care purchased by families were also collected in the survey. When this information was available, direct expenditure paid by individuals was calculated. For individuals who did not declare their expenditure for home-based care, the costs used were obtained from published sources for the cost of domiciliary nursing care in the UK[125] or extrapolated costs obtained from other patients in the sample for other types of specific home help (for example, for gardeners). Since insufficient information was obtained on costs of family care, these costs were not considered in the analysis.

The cost of travel to and from GP surgeries and hospitals was included in the analysis of societal costs. The unit cost of travel to and from the GP surgery and hospital was estimated using data collected for a study that used patient diaries to cost travel for day case and outpatients visits for women with hysteroscopy.[129] This study reported a travel cost for an outpatient visit of £3.50 and for a day case £6; these figures were adjusted to 2005 costs. An average of £3.50 was allowed for each GP visit.

Possible societal costs not included are cost of reaching healthcare facilities for testing, cost of reaching pharmacy to collect drugs and over-the-counter drugs costs. Since the majority of the participants are retired, changes in carer employment status and income or work-related and productivity issues have not been included. Although data were available on the employment status of the carer, carer's time taken to attend clinics was not included, because of the difficulties in collecting accurate data.

EQ-5D and utilities

Quality of life was assessed for the cost-effectiveness analysis using the EQ-5D.[130] Participants completed questionnaires at baseline and 3, 6, 12 and 24 months of follow-up. EQ-5D questionnaires are self-assessed quality of life instruments, in which quality of life is measured using five questions on mobility, self-care, performing usual activities, pain or discomfort and anxiety or depression. For each of these questions, the responder can choose one of three possible answers, among 'No problems', 'Some problems' or 'Unable' to carry out the relevant task or activity.[130]

Analysis

Costs from the NHS–PSS perspective

Total NHS costs were calculated for each participant adding the cost of consultations, diagnostic and blood tests, admissions, equipment, rehabilitation and physiotherapy services and prescriptions. For each cost category, the number of items or contacts with each type of healthcare service was multiplied by their unit cost.

Admissions in the study were assigned a cost from the NHS Reference Cost Database,[126] matching the cause of admissions as coded in discharge letters to the corresponding Health Resource Group (HRG). Unit costs were stratified for day cases and, for longer admissions, for elective and non-elective admissions; we used general medical admission averages where data on cause of admission could not be coded.

In the Reference Cost Database, costs are based on the average length of stay for all admissions in the relevant HRG.[126] For the participants, data on length of stay were available. Admissions with duration of less than 1 day were costed using unit costs for day cases from the database. For individuals with at least one overnight stay, and since costs from this source are not presented disaggregated by length of stay, the average cost and length of stay for any admission type was used. The use of national averages for length of stay may improve the generalisability of the results of this cost–utility analysis. We considered the impact of the difference between average and actual length of stay for individuals in the sample in a sensitivity analysis. In this alternative analysis, we conducted a set of regression analyses of costs on length of stay on the reference cost database data, for each HRG. With this regression, an imputed cost of admission was calculated based on actual length of stay for individuals in the trial.

Prescription costs were calculated by multiplying acquisition costs by the number of items prescribed for each prescription. The cost of over-the-counter preparations was not included in NHS costs.

The cost of equipment and aids was calculated by multiplying number of items used by their unit cost. Items both dispensed by the NHS and purchased privately were included in NHS costs limited to the items declared as 'dispensed from the NHS' or 'dispensed for free'. For individuals who did not recall this information, the items were assumed to have been purchased privately.

Costs from the societal perspective

Total costs were calculated from a societal perspective. This perspective included all NHS costs and, in addition, the cost of all privately purchased items and the cost of care purchased by families.

The total cost of privately purchased equipment and aids was obtained by multiplying quantity by price paid, as declared by participants. For individuals who were unable to recall this information, the mean unit price paid was extrapolated to estimate the cost of similar items.

In the calculation of costs, we did not include productivity costs relative to potential income losses for the patients, or their carers, due to disease or treatment.

Quality-adjusted life-years

QALYs were calculated from EQ-5D data. Responses from the EQ-5D questionnaires were transformed into quality of life weights (utility) using an econometric model developed by Dolan and colleagues with reference to the UK general population.[130] The specification of this model is reported in Appendix 3.

Total utility was calculated for each participant from point estimates at baseline and 3, 6, 12 and 24 months, using the area under the curve (AUC). To estimate the total utility, some inference is needed about the utility of a person between these point estimates. It was assumed that between the point estimates, a person's utility was the average of two consecutive utility measures. These utility estimates were then simply added up taking into account the length of time between measurements.

For patients with incomplete or missing quality of life questionnaires, between two non-consecutive time-points simple interpolation was used to assign a quality of life score.

Analysis of cost and quality of life data

Mean total costs were calculated for topical and oral ibuprofen for each participant, from both an NHS and a societal perspective.

Mean incremental costs were then calculated and mean incremental QALYs for the groups allocated to topical or oral ibuprofen using inverse probability weighting in a regression framework. Inverse probability weighting is well described.[131] The use of inverse probability weighting was motivated since, although no significant predictor was found for length of follow-up in the study and there were no deaths during the study period, individuals in general accrue costs at different rates. The same justification applies to the weighting of QALYs.

A regression framework was used to calculate incremental costs and QALYs adjusted for prognostic factors for both the RCT and PPS, and in particular to enable adjustments in the PPS with respect to potential baseline imbalances in gender and age. This was because participation into the PPS was motivated by patient preferences, which were informed by the participant's perceived health status at entry into the study. The explicit consideration of baseline differences in gender and age allowed us to control for the impact on the cost-effectiveness of self-selection into the PPS and into each type of treatment.

To investigate the variation around the ICER, we chose to use non-parametric bootstrapping methods. These have been used to describe the effect of variations around the ICER.[123] The bootstrap method involves randomly selected 1000 samples of costs and QALYs of individuals in number equal to the participants in each study. Mean incremental costs and QALYs are calculated for each sample and then plotted on a graph, the cost-effectiveness plane.

Cost–utility

The cost–utility of topical ibuprofen was assessed using the mean incremental cost and QALYs associated with allocation to the topical group in each study, in comparison with allocation to the oral group. The mean incremental cost of allocation to the topical group, resulting from the regression framework, was compared with the mean incremental quality-adjusted survival gain. Cost–utility ratios were calculated separately for the RCT and the PPS. Two different time horizons were used: 12 months to match the primary analysis of the effectiveness study and 24 months to make the maximum use of our available data. The 12-month analyses are the primary health economic analysis.

In general, the cost–utility ratio is a measure of the relative cost per unit improvement in quality-adjusted life expectancy from being in an oral rather than a topical group. Topical administration would be cost-effective if individuals, on average, had lower costs and better outcomes with this route of administration. This combination of costs and outcomes is termed 'dominant'. In cases where both the total cost in the topical group and total outcomes are higher compared with the oral group, cost-effectiveness is a relative judgement, requiring that the cost–utility ratio is lower than the 'acceptability' or 'willingness to pay' threshold. This is a monetary value that a hypothetical decision-maker is willing to pay for one QALY obtained from advising the use of a topical NSAID.

Since a definite threshold has empirically proven difficult to set, an assessment was made of the cost–utility of advice to use topical NSAIDs using willingness to pay thresholds ranging between £0 and £40,000.[132] For each of these values, a net benefit statistic was calculated. This is the difference between the total cost of the intervention and the total value of health gain, calculated as the total number of QALYs multiplied by the monetary valuation of one QALY, assumed equal to the acceptability threshold.

Using the results of the bootstrap procedure, the probability was then calculated that topical ibuprofen was cost-effective using the relative frequency of dominant or cost-effective combinations of costs and health outcomes for each willingness-to-pay threshold. This probability was presented using a cost-effectiveness acceptability curve (CEAC), that is, the graphical representation of the cumulative probability that topical ibuprofen was cost-effective for each value of the willingness-to-pay threshold.

Sensitivity analyses

To assess the robustness of the analysis to changes of some input values or assumptions, the cost-effectiveness analyses were run using alternative scenarios for some cost items. The following were considered:

1. unit costs and cost of admissions based on actual length of stay reported in discharge notes
2. excluding high-cost individuals (95th percentile of total cost of care at 12 months)
3. including the total cost of drugs prescribed during the study period, including any not directly related to knee OA or pain and potential side-effects
4. increasing the discount rate to 6%.

Subgroup analyses

In initial analyses, it was found that age and gender both affected costs and QALYs. Therefore, subgroup analyses were carried out to estimate the ICERs for these subgroups in both the RCT and PPS. Initially, a separate assessment of the cost–utility analysis for compliant individuals had also been planned. However, since compliance was very good, this analysis was not considered any further.

Results

The study population's mean age was 63 years in the RCT and 66 years in the PPS. Over half of the participants were female, 53% in the RCT (56% oral and 51% topical) and 58% in the PPS (61% oral and 57% topical). There was no difference by gender in the mean age of participants.

Mean follow-up for the calculation of costs and QALYs was 517 days for the RCT (oral 510, topical 525 days) and in the PPS it was 591 days (oral 629, topical 577 days). In a univariate analysis, the difference in length of follow-up in the two arms of the PPS was of borderline

statistical significance ($p = 0.054$). After controlling for differences in gender and age at baseline, the difference in length of follow-up was still of borderline significance ($p = 0.048$).

Data on costs and quality of life were available for approximately 85% of individuals at the end of 12 months and 66% at 24 months.

Quality of life scores (EQ-5D)

Quality of life scores (EQ-5D) were available for a total of 576 participants at baseline, 524 at 3 months, 504 at 6 months, 488 at 12 months and 382 participants at the end of 24 months of follow-up (*Table 77*). Over 80% of participants had complete health economic follow-up data at the end of 12 months. The gain in QALYs was calculated using an inverse weighting approach in both the RCT and the PPS.

Utility scores

Utility scores were calculated from EQ-5D scores using an algorithm developed by Dolan and colleagues.[130] Overall, there were no differences in utility scores by treatment allocation at each measurement, either in the RCT or in the PPS. No statistically significant differences were found between the score at baseline and the score at 12 months (*Table 78*, *Figures 29* and *30*; the graphs show data only for those with a full utility score record).

There were no differences in utility at baseline by gender (RCT: males 0.65, female 0.67, $p = 0.27$; PPS: males 0.65, females 0.65, $p = 0.94$). However, a participant's age at baseline significantly affected the differences observed between utilities at baseline and 6 months and at baseline and 12 months. For each additional year difference in a participant's age at baseline, their utility decreased by 0.003 between baseline and 12 months ($p = 0.008$).

Quality-adjusted life-years

We calculated QALYs using the average of two consecutive utility measurements weighted by time between the two measurements (*Table 79*). Overall, QALY gains were better for those in the oral groups, although the differences were small or very small in both studies. In the RCT, the mean difference in QALYs was 0.007 at 12 months and was further reduced to 0.002 at 24 months. In the PPS, the loss in QALYs with topical ibuprofen was slightly larger, 0.04 at 12-months and 0.105 at 24-months. These results are crude differences between QALY scores and are not obtained from the inverse weighting analysis. They should therefore only be considered an illustration of the data used in the cost-effectiveness analysis and are presented only for completeness.

NHS and PSS costs

Resource consumption

Drug costs

In the RCT, the total cost of drugs was lower in the topical group (*Table 80*). Individuals in the PPS reported a remarkably similar total expenditure in drugs at 12-months of follow-up, but the cost of drugs was greater in the topical group over 24 months (*Table 81*). As expected, the overall cost of oral ibuprofen was lower than that of topical ibuprofen. The cost of study drugs was a relatively

TABLE 77 *Number of individuals with complete EQ-5D and follow-up cost data*

	RCT		PPS	
	Oral *n* = 144	Topical *n* = 138	Oral *n* = 78	Topical *n* = 225
Baseline	140	138	78	220
3 months	132	127	71	194
6 months	125	118	66	195
12 months	119	116	68	185
24 months	78	81	64	159

TABLE 78 *EQ-5D utility scores*

	RCT				PPS			
	Oral	Topical	Difference[a]	*N*	Oral	Topical	Difference[a]	*N*
Baseline	0.648	0.670	+0.022	278	0.633	0.656	+0.023	298
3 months	0.657	0.660	+0.003	259	0.647	0.647	+0.000	265
6 months	0.653	0.637	–0.016	243	0.634	0.647	+0.003	261
12 months	0.662	0.650	–0.012	235	0.643	0.629	–0.013	253
24 months	0.676	0.684	–0.008	159	0.622	0.607	–0.015	223

[a] Negative values indicate topical is worse.

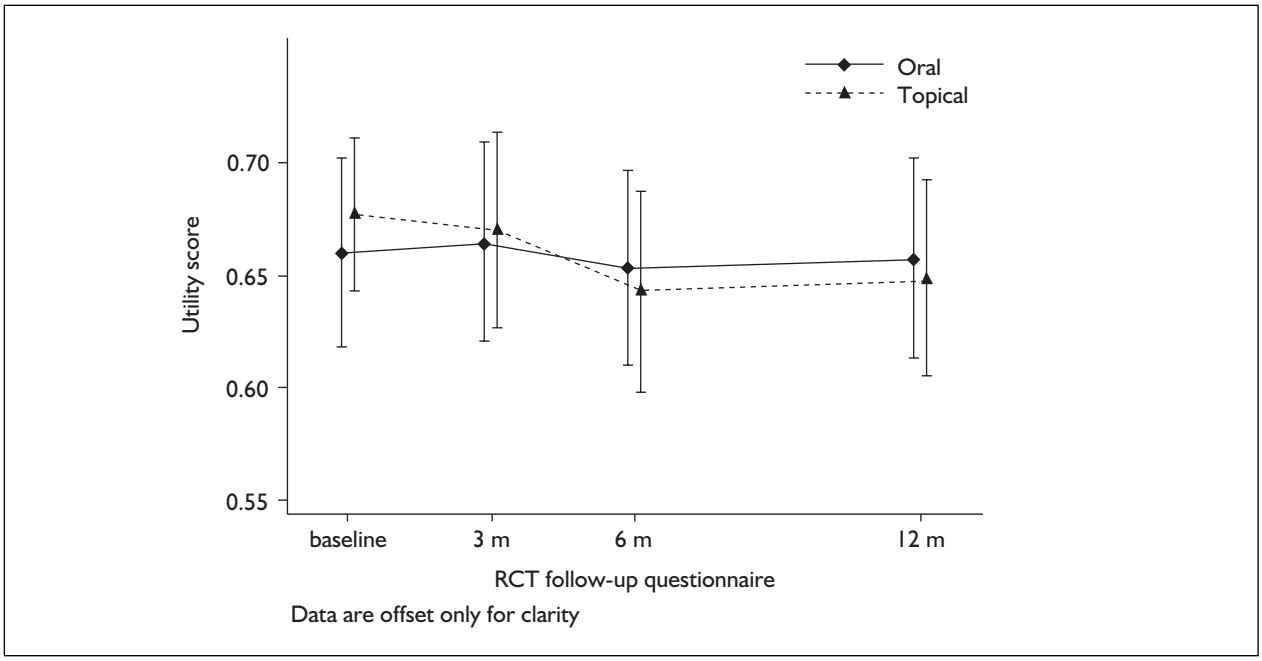


FIGURE 29 *Utility score, RCT*

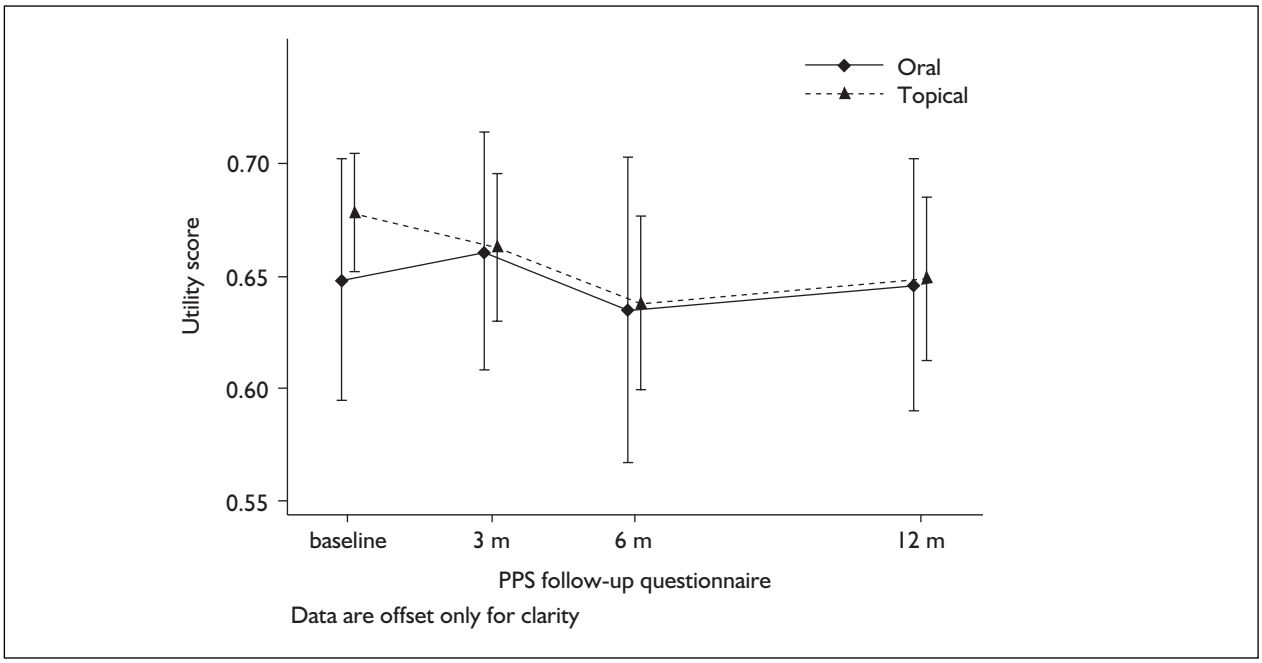


FIGURE 30 *Utility score, PPS*

modest proportion of the total cost of drugs over the course of the study, particularly for oral ibuprofen. Reassuringly, there were large, and statistically significant, differences in the cost of oral and topical NSAIDs between the two groups in both the RCT and the PPS.

Although topical NSAIDs have a higher initial cost, the cost of oral NSAIDs for those in the topical groups was higher than the cost of topical NSAIDs for those in the oral groups in the RCT. However, in the PPS, individuals in the oral group also had higher costs for oral NSAIDs.

In all groups, the costs of oral ibuprofen were lower than the costs of other oral NSAIDs. This is most marked in the PPS. This is because a small number of participants were prescribed more expensive oral NSAIDs in preference to ibuprofen.

TABLE 79 *Total mean crude QALYs accrued, by study and length of follow-up*

	RCT		PPS	
	Oral	**Topical**	**Oral**	**Topical**
Total QALY, crude estimate, 12 months	0.628	0.621	0.634	0.594
Total QALY, crude estimate, 24 months (discounted)[a]	0.934	0.932	1.090	0.985

[a] QALYs that occurred in the second year were discounted to take account of the slightly lower weight given to costs and effects that occur in the future. The costs and effect in our study were both discounted at a rate of 3.5% as recommended by HM Treasury. Hence in our calculations QALYs calculated in the 12 months are assumed to have a weight of 1, and QALYs in the second year have a weight of 0.966, i.e. 1/(1.035) = 0.966).

TABLE 80 *Drug costs, by drug type, RCT*

Drug type	**12 months**				**24 months**			
	Oral (£)	**Topical (£)**	**Topical – oral (£)**	***p*-Value**	**Oral (£)**	**Topical (£)**	**Topical – oral (£)**	***p*-Value**
Oral ibuprofen	9.16	0.78	–8.38	0.00	15.66	1.19	–14.47	0.00
Other oral NSAIDs	9.00	11.97	2.97	0.53	7.04	20.69	13.65	0.25
Topical ibuprofen	0.32	19.61	19.29	0.00	0.22	26.72	26.49	0.00
Other topical NSAIDs	0.56	0.04	–0.52	0.20	0.71	0.00	–0.71	0.30
Other topicals	0.14	0.16	0.03	0.85	0.23	0.19	–0.04	0.86
Paracetamol	6.56	4.49	–2.07	0.13	13.45	9.23	–4.22	0.14
Aspirin	1.06	0.87	–0.19	0.39	0.94	2.14	1.20	0.20
Mild opioids	0.79	0.01	–0.78	0.29	0.06	0.00	–0.06	0.50
Strong opioids	3.07	1.31	–1.75	0.73	8.70	0.80	–7.90	0.31
Cardiovascular drugs	55.42	31.83	–23.59	0.08	82.83	43.01	–39.82	0.08
Indigestion and gastrointestinal	16.54	12.31	–4.23	0.47	35.15	15.02	–20.13	0.17
Respiratory drugs	0.11	0.05	–0.07	0.59	0.23	0.08	–0.16	0.47
Total relevant drugs	**102.73**	**83.44**	**–19.30**	**0.28**	**165.22**	**119.05**	**–46.17**	**0.19**
Other drugs	165.12	108.84	–56.28	0.13	217.24	159.26	–57.98	0.26
Total all drugs	**267.85**	**192.28**	**–75.58**	**0.12**	**382.47**	**278.31**	**–104.15**	**0.17**

TABLE 81 *Drug costs, by drug type, PPS*

Drug type	**12 months**				**24 months**			
	Oral (£)	**Topical (£)**	**Topical – oral (£)**	***p*-Value**	**Oral (£)**	**Topical (£)**	**Topical – oral (£)**	***p*-Value**
Oral ibuprofen	11.51	0.78	–10.72	0.00	17.73	1.80	–15.93	0.00
Other oral NSAIDs	13.47	4.16	–9.31	0.04	25.14	10.36	–14.78	0.02
Topical ibuprofen	0.00	22.89	22.89	0.63	0.00	33.37	33.37	0.00
Other topical NSAIDs	0.00	0.00	0.00	0.14	0.05	0.10	0.05	0.00
Other topicals	0.86	0.06	–0.80	0.00	1.35	0.35	–1.00	0.03
Paracetamol	9.33	6.06	–3.27	0.33	12.13	8.93	–3.20	0.79
Aspirin	0.95	1.14	0.19	0.73	1.57	2.10	0.53	0.93
Mild opioids	0.12	0.22	0.10	0.22	0.11	1.05	0.94	0.12
Strong opioids	3.98	3.69	–0.29	0.51	5.22	7.19	1.97	0.67
Cardiovascular drugs	46.56	48.03	1.47	0.53	68.42	83.52	15.10	0.91
Indigestion and gastrointestinal	8.40	9.31	0.91	0.16	7.79	20.71	12.92	0.83
Respiratory drugs	0.00	0.02	0.02	0.20	0.00	0.05	0.05	0.40
Total relevant drugs	**95.18**	**96.36**	**1.18**	**0.94**	**139.50**	**169.51**	**30.01**	**0.31**
Other drugs	112.45	141.49	29.04	0.51	181.98	271.93	89.95	0.28
Total all drugs	**207.63**	**237.85**	**30.22**	**0.55**	**321.48**	**441.44**	**119.96**	**0.21**

The higher overall cost of drugs in participants in the RCT oral groups was largely due to a greater cost for cardiovascular drugs. At the end of 24 months' follow-up, the cost of cardiovascular drugs in this group was double that for participants in the RCT topical group. This difference is of borderline statistical significance. There was no comparable excess cost for cardiovascular drugs in the PPS, despite individuals in the PPS being prescribed more DDDs of oral NSAIDs than any of the other groups. Similarly, in the RCT the cost of gastrointestinal and indigestion drugs was higher in individuals treated in the oral group, although this difference was not statistically significant.

Cost of care

The average total cost of care was lower in the topical group, over both 12 and 24 months in the RCT and over 12 months in the PPS (*Tables 82* and *83*). However, individuals in the PPS topical group had a higher cost of care over 24 months than the PPS oral group. The cost of all major groups of healthcare consumption was lower with topical ibuprofen, with the exception of the cost of GP and outpatient consultations, equipment and aids and, in the PPS, diagnostic tests. These differences were very small in absolute values. None of these differences were statistically significant.

Differences between RCT and PPS

Overall, the cost of care for individuals in the RCT was lower than that for individuals in the PPS. These differences in costs between RCT and PPS increased in the longer term. In particular, the cost of care in the PPS remained higher than that of individuals in the RCT topical group, but not those in the RCT oral group.

Predictors of costs

The main cost-effectiveness analysis looked at the cost-effectiveness of the treatment for the study population as a whole. However, it was also important to consider whether the treatment is cost-effective for subsamples of this population. Here we consider the main predictors of costs and if these predictors lead to significant differences in costs between the study arms where they may cause differences in the cost-effectiveness calculation.

When considering what factors to use in our subgroup analysis, we restricted ourselves to characteristics, such as age and gender, which are easily identifiable and which can be used by policy makers to define the entry criteria for treatment.

In both the RCT and PPS, it was found that the majority of costs were significantly higher for

TABLE 82 *Cost of care, by type of service, RCT*

Type of service	12 months				24 months			
	Oral (£)	Topical (£)	Topical – oral (£)	*p*-Value	Oral (£)	Topical (£)	Topical – oral (£)	*p*-Value
GP and nurse consultations	140	133	–7	0.66	223	259	36	0.20
Outpatient consultations	79	58	–21	0.10	122	133	11	0.67
Diagnostic tests	19	13	–6	0.58	26	21	–5	0.41
Equipment and aids	9	3	–6	0.18	7	2	–5	0.18
Hospital admissions	477	354	–123	0.62	663	491	–172	0.54
Prescription costs (all)	103	83	–19	0.29	165	119	–46	0.20
Total	**826**	**644**	**–182**	**0.47**	**1206**	**1025**	**–181**	**0.56**

TABLE 83 *Cost of care, by type of service, PPS*

Type of service	12 months				24 months			
	Oral (£)	Topical (£)	Topical – oral (£)	*p*-Value	Oral (£)	Topical (£)	Topical – oral (£)	*p*-Value
GP and nurse consultations	131	138	8	0.63	236	238	2	0.92
Outpatient consultations	61	72	11	0.44	102	123	21	0.33
Diagnostic tests	20	23	3	0.46	25	33	8	0.18
Equipment and aids	1	3	1	0.61	2	5	4	0.30
Hospital admissions	507	361	–146	0.46	616	809	193	0.40
Prescription costs (all)	95	96	1	0.94	140	170	30	0.31
Total	**815**	**693**	**–122**	**0.57**	**1120**	**1378**	**258**	**0.38**

older individuals and for men: older individuals were defined as those with an age higher than the median age in our study. For example, in the RCT older people had significantly higher costs for GP and nurse consultations ($p = 0.002$), testing and diagnosis ($p = 0.049$) and drugs ($p = 0.001$). The cost of topical ibuprofen was significantly higher in older people overall ($p = 0.02$).

In the PPS, males had significantly higher costs for admissions ($p = 0.036$), drugs ($p = 0.031$) and topical NSAIDs ($p = 0.034$), and nearly significantly higher total care ($p = 0.065$). The cost for topical ibuprofen was higher in males ($p = 0.022$) and nearly statistically significant in older people ($p = 0.056$) regardless of allocation.

The cost of oral ibuprofen was higher for males than females in the RCT at 24 months' follow-up ($p = 0.026$), controlling for allocation and age, although a statistically significant difference was not detected in costs of the intervention drug by gender at 12 months (ibuprofen, $p = 0.08$).

It was found that age and gender may both affect costs and health utility within this study. These findings, drawn on easily available factors that could be used to inform policy, serve to inform the inverse weighting of the final cost-effectiveness model; they not a substitute for a carefully conducted cohort study for predictors of outcome for older people.

Patients and family costs

Resource consumption

Significant patient and family costs for the care of knee pain were identified (*Tables 84* and *85*). This was in spite of us not including carer's costs and loss of income. We have probably underestimated the overall cost of social care for the participants. Nevertheless, the costs identified were in the range £180–310 per participant over the first year.

TABLE 84 *Type and cost of privately purchased services or family care, RCT*

Type of healthcare service or contact	12 months				24 months			
	Oral (£)	Topical (£)	Topical – oral (£)	*p*-Value	Oral (£)	Topical (£)	Topical – oral (£)	*p*-Value
Private healthcare costs, GP and nurse visits, outpatient consultations	84	64	–20	0.62	238	114	–124	0.24
Hospital admissions	76	50	–25	0.63	104	137	33	0.74
Equipment and aids, private purchases	90	12	–77	0.24	160	11	–149	0.19
Domiciliary help, including family care or other care	27	24	–3	0.82	46	37	–9	0.72
Transport costs	31	28	–3	0.49	49	57	8	0.71
Total	**308**	**178**	**–128**	**0.21**	**597**	**356**	**–241**	**0.19**

TABLE 85 *Type and cost of privately purchased services or family care, PPS*

Type of healthcare service or contact	12 months				24 months			
	Oral (£)	Topical (£)	Topical – oral (£)	*p*-Value	Oral (£)	Topical (£)	Topical – oral (£)	*p*-Value
Private healthcare costs, GP and nurse visits, outpatient consultations	48	29	–19	0.37	83	31	–52	0.05
Hospital admissions	152	61	–91	0.26	251	86	–166	0.16
Equipment and aids, private purchases	2	43	41	0.35	4	58	54	0.32
Domiciliary help, including family care or other care	28	39	11	0.47	35	63	28	0.25
Transport costs	54	53	–1	0.82	56	58	2	0.71
Total	**284**	**225**	**–59**	**0.58**	**429**	**296**	**–133**	**0.36**

Across both studies these costs were greater over both 12- and 24-month time horizons in the oral group. The difference was £128 per participant over 12 months in the RCT and over £59 in the PPS. To put this difference into context, the differences in NHS costs over 12 months were £182 and £122 in the RCT and PPS, respectively. Hence, differences in personal cost between the two treatment approaches may be of a similar magnitude to the differences in NHS costs and need to be considered in any decision on advising oral or topical NSAIDs. No obvious pattern emerges from the data as to which components of our costs explain these differences in participant and family costs.

Cost-effectiveness of topical ibuprofen, NHS perspective

Total incremental costs and total incremental QALYs

The incremental cost and effect were analysed using inverse probability weighted regressions, controlling for differences in baseline covariates.[131] Inverse weighting regression is used particularly when there are reasons to believe that costs and QALYs may be accrued at different rates by different individuals.

Mean incremental costs and QALYs were calculated as the mean coefficient in a regression for the treatment term. A regression approach also allowed adjustment of estimates for mean costs and QALYs by participant characteristics that may predict costs or changes in quality of life. Incremental costs and QALYs were calculated controlling for gender (males) and age (above median age in each substudy, 60 years in the RCT and 65 years in the PPS), as these factors were identified as significant in the descriptive analysis. In addition, the estimate for incremental QALYs for utility measured at baseline was adjusted since this was a significant predictor of changes in utility during follow-up. This was because whereas the potential baseline differences in the RCT may have been resolved by randomisation, the PPS was likely to have baseline imbalances in quality of life; this factor was probably one of the very reasons underpinning a preference for oral or topical treatment.

Five different specifications of the regression model were considered: treatment alone; treatment and age; treatment and gender; treatment, age and gender; and treatment, age, gender and an interaction term for age and gender.

These predictors were entered into the regression as dummy variables. For example, in the regressions with one predictor, age, the variables were coded as 0 for females and 1 for males. For the regression with two predictors, age and gender, the variables were coded 1 (above median age, male) or 0 (below median age, female).

The models specified are shown in *Tables 86–89*. The column headings report the models considered. The first column details the coefficient calculated for each model, with corresponding values for the coefficients in each row. A bootstrap procedure was then conducted, repeated 1000 times, and mean coefficients were estimated for each of these regressions, which are reported below.

In each column, incremental costs and incremental effects for treatment are estimated. These are the coefficient of costs and QALYs regressed on the 'treatment' term. The interpretation of these coefficients is straightforward, with negative values indicating that topical is less costly and less effective, and the ratio of these two coefficients is the ICER for topical ibuprofen. In each model, the ICER for treatment ('Incremental cost topical ibuprofen' divided by 'Incremental QALY topical ibuprofen') can be calculated given the relevant set of covariates considered, and is interpreted as the ICER for topical ibuprofen adjusted by the relevant covariates. The coefficients for age, gender and the interaction term are interpreted as the mean incremental cost for each of the predictors. For each subgroup then, the mean incremental cost is equal to the mean incremental cost of treatment summed to the mean incremental cost for the subgroup of interest, that is, males.

Using these derived estimates, the ICER by subgroups can be calculated for all subgroups considered in each model. For example, in the RCT at 12 months' follow-up, in the model including gender alone (*Table 86*), the incremental cost for topical ibuprofen is –£184.3 and the incremental QALY is –0.021. In this model, being male is associated with an incremental cost of approximately –£230 and incremental QALYs equal to –0.026. This means that in males, in the RCT at 12 months, total incremental costs and effects in the topical group are still lower than with oral ibuprofen. In models with more than one predictor, each coefficient can be used to calculate the relevant ICER for the subgroup of interest,

while the adjusted ICER for treatment overall remains defined as above.

At 12 months, topical groups had lower total cost in both the RCT and the PPS. Being male was also associated with lower costs in the RCT topical group, but not in the PPS topical group. However, older age was a predictor of higher cost in the topical groups.

At 24 months, the costs were lower in the RCT topical group but not in the PPS topical group, for most regressions, but not for older age. For this group, the incremental costs associated with topical ibuprofen were large.

The topical groups had lower QALYs in almost all models specified, at both 12 and 24 months, with a slightly larger loss in QALY in the PPS. The difference increased with time, in similar proportions in the RCT and in the PPS. However, surprisingly, males reported a gain in QALYs with topical ibuprofen at 24 months in the RCT.

Incremental cost-effectiveness ratios (ICERs)

ICERs were calculated overall and by subgroups identified in the regression framework. These are presented in *Tables 90–93*. ICERs from the NHS perspective were calculated by dividing the difference in costs between the groups by the difference in QALYs accrued by the two groups. The ICER measures the relative cost of acquiring one additional QALY with topical treatment.

Since both costs and QALYs were reduced with topical compared with oral ibuprofen, the ICERs indicate that oral treatment was cost-effective with an ICER at 12 months ranging, in all models specified, between £8600 and £9100 for the RCT and between £2000 and £3200 for the PPS (*Tables 90* and *92*).

TABLE 86 *Model specifications for incremental costs and QALYs adjusted for baseline covariates, RCT, 12 months*[a]

Parameter	Model				
	No covariates	Gender alone (males)	Age alone (older than median age)	Age and gender	Age, gender and interaction
Incremental costs, topical (£)	–176.2	–184.3	–181.6	–173.521	–191.4
Incremental cost, males (£)	–	–50.7	–	–48.7	–64.7
Incremental costs, older people (£)	–	–	364.7	361.3	336.3
Incremental cost, older males (£)	–	–	–	–	38.6
Incremental effects, topical	–0.020	–0.021	–0.020	–0.021	–0.021
Incremental effects, males	–	–0.005	–	–0.005	–0.002
Incremental effects, older people	–	–	–0.053	–0.053	–0.052
Incremental cost, older males	–	–	–	–	–0.006

[a] Negative values indicate topical is less costly and less effective.

TABLE 87 *Model specifications for incremental costs and QALYs adjusted for baseline covariates, RCT, 24 months*[a]

Parameter	Model				
	No covariates	Gender alone (males)	Age alone (older than median age)	Age and gender	Age, gender and interaction
Incremental costs, topical (£)	–420.5	–404.6	–467.6	–421.5	–455.1
Incremental cost, gender (£)	–	–369.1	–	–297.0	–94.9
Incremental costs, age (£)	–	–	841.5	783.9	889.1
Incremental cost, age × gender (£)	–	–	–	–	–299.6
Incremental effects, topical	–0.027	–0.028	–0.026	–0.031	–0.038
Incremental effects, gender	–	0.026	–	0.033	0.094
Incremental effects, age	–	–	–0.037	–0.030	0.009
Incremental cost, age × gender	–	–	–	–	–0.101

[a] Negative values indicate topical is less costly and less effective.

TABLE 88 *Model specifications for incremental costs and QALYs adjusted for baseline covariates, PPS, 12 months*[a]

Parameter	Model				
	No covariates	**Gender alone (males)**	**Age alone (older than median age)**	**Age and gender**	**Age, gender and interaction**
Incremental costs, topical (£)	–64.8	–60.1	–86.2	–69.2	–71.8
Incremental cost, gender (£)	–	273.8	–	263.4	125.5
Incremental costs, age (£)	–	–	227.9	208.1	119.2
Incremental costs, age × gender (£)	–	–	–	–	230.4
Incremental effects, topical	–0.028	–0.029	–0.027	–0.027	–0.028
Incremental effects, gender	–	–0.025	–	–0.024	–0.019
Incremental effects, age	–	–	–0.017	–0.014	–0.012
Incremental effect, age × gender	–	–	–	–	–0.008

[a] Negative values indicate topical is less costly and less effective.

TABLE 89 *Model specifications for incremental costs and QALYs adjusted for baseline covariates, PPS, 24 months*[a]

Parameter	Model				
	No covariates	**Gender alone (males)**	**Age alone (older than median age)**	**Age and gender**	**Age, gender and interaction**
Incremental costs, topical (£)	152.08	–143.58	50.8	4.6	33.1
Incremental cost, gender (£)		–114.15	–	–207.2	198.1
Incremental costs, age (£)	–	–	1009	1089.7	1335.0
Incremental cost, age × gender (£)	–	–	–	–	–552.2
Incremental effects, topical	–0.04	–0.039	–0.031	–0.035	–0.037
Incremental effects, gender	–	–0.045	–	–0.042	–0.094
Incremental effects, age	–	–	–0.046	–0.042	–0.074
Incremental cost, age × gender	–	–	–	–	0.076

[a] Negative values indicate topical is less costly and less effective.

TABLE 90 *ICERs with topical compared with oral ibuprofen, RCT, 12 months (adjusted for censoring and covariates)*

	Model				
	No covariates	**Gender alone (males)**	**Age alone (older than median age)**	**Age and gender**	**Age, gender and interaction**
ICER (£)	8,810	8,782	9,080	8,263	9,114
ICER, males (£)	–	9,043	–	8,547	11,135
ICER, age above median (£)	–	–	Oral dominant, 183.1,[a] –0.073[b]	Oral dominant, 187.8,[a] –0.074[b]	Oral dominant, 144.9,[a] –0.073[b]
ICER, males, age above median (£)	–	–	–	–	Oral dominant, 119,[a] –0.081[b]

[a] Cost difference in £. Positive differences = topical more expensive.
[b] QALY difference. Positive differences = topical more effective.

At 24 months, the ICERs became less favourable in the RCT, with oral treatment remaining cost-effective in the RCT, with ICERs between £12,000 and £18,000. In most cases in the PPS, oral NSAIDs clearly became dominant, that is, topical treatment was less effective and more costly. This was because of an increase in the incremental cost for topical ibuprofen over this time horizon. In the RCT, there was a perhaps surprising inversion of this trend, with topical ibuprofen becoming more cost-effective (i.e. oral being very cost-ineffective) and even dominant in males, depending on the

TABLE 91 *ICERs with topical compared with oral ibuprofen, RCT, 24 months (adjusted for censoring and covariates)*

	Model				
	No covariates	**Gender alone (males)**	**Age alone (older than median age)**	**Age and gender**	**Age, gender and interaction**
ICER (£)	15,574	14,450	17,985	13,597	11,976
ICER, males (£)	–	386,850	–	Topical dominant, –718.5,[a] 0.002[b]	Topical dominant, –549.9,[a] 0.056[b]
ICER, age above median (£)	–	–	Oral dominant, 373.8,[a] –0.063[b]	Oral dominant, 362.4,[a] –0.062[b]	Oral dominant, 434.0,[a] –0.030[b]
ICER, males, age above median (£)	–	–	–	–	Oral dominant, 39.5,[a] –0.036[b]

[a] Cost difference in £. Positive differences = topical more expensive.
[b] QALY difference. Positive differences = topical more effective.

TABLE 92 *ICERs with topical compared with oral ibuprofen, PPS, 12 months (adjusted for censoring and covariates)*

	Model				
	No covariates	**Gender alone (males)**	**Age alone (older than median age)**	**Age and gender**	**Age, gender and interaction**
ICER (£)	2314	2072	3193	2563	2564
ICER, males (£)	–	Oral dominant, 213.7,[a] –0.054[b]	–	Oral dominant, 194.2,[a] –0.051[b]	Oral dominant, 53.7,[a] –0.047[b]
ICER, age above median (£)	–	–	Oral dominant, 130.9,[a] –0.044[b]	Oral dominant, 138.9,[a] –0.041[b]	Oral dominant, 47.4,[a] –0.04[b]
ICER, males, age above median (£)	–	–	–	–	Oral dominant, 403.4,[a] –0.0678[b]

[a] Cost difference in £. Positive differences = topical more expensive.
[b] QALY difference. Positive differences = topical more effective.

TABLE 93 *ICERs with topical compared with oral ibuprofen, PPS, 24 months (adjusted for censoring and covariates)*

	Model				
	No covariates	**Gender alone (males)**	**Age alone (older than median age)**	**Age and gender**	**Age, gender and interaction**
ICER (£)	Oral dominant, 152.8,[a] –0.037[b]	3682	Oral dominant, 51,[a] –0.031[b]	Oral dominant, 5,[a] –0.035[b]	Oral dominant, 33,[a] –0.037[b]
ICER, males (£)	–	3068	–	2633	Oral dominant, 231,[a] –0.13[b]
ICER, age above median (£)	–	–	Oral dominant, 1060,[a] –0.077[b]	Oral dominant, 1094,[a] –0.077[b]	Oral dominant, 1,368,[a] –0.11[b]
ICER, males, age above median (£)	–	–	–	–	Oral dominant, 1014,[a] –0.13[b]

[a] Cost difference in £. Positive differences = topical more expensive.
[b] QALY difference. Positive differences = topical more effective.

specification of the model. In either case, there was a clear indication that topical ibuprofen reduced costs and improved QALYs in the male group, albeit limited at 24 months.

Being older was an independent predictor of increased healthcare cost in both the RCT and the PPS. However, being male was in some cases associated with reduced costs and better outcomes. Although these data should be interpreted with caution, they do show how sensitive the direction of change in QALYs and cost may be, with the direction of dominance changing towards oral ibuprofen in the PPS and oral medication not being dominant, or in some cases becoming dominated, in males. There is a suggestion from these data that at least on economic grounds, oral or topical NSAIDs may be more or less appropriate for different types of patients. This observation is, however, no more than hypothesis generating. The costs and QALYs in *Tables 90–93* are 'incremental' costs and QALYs for the subgroups identified in the cost-effectiveness analysis where one treatment approach was dominant. These coefficients are derived from a regression of costs and QALYs, adjusted for age and for gender, separately and for age and gender jointly considered. QALYs are also adjusted for utility at baseline.

A sensitivity analysis was carried out to explore the impact of some assumptions on the ICERs. Overall, the results appear similar to the results of the main analysis (*Table 94*).

Cost-effectiveness planes

To assess the impact of variations on the estimates of the ICER, we randomly selected 1000 samples of costs and QALYs of individuals in number equal to the participants in each study. Mean incremental costs and QALYs were calculated for each sample and were then plotted on a graph, the cost-effectiveness plane. This was a representation of the joint incremental cost and QALY obtained with the bootstrap procedure, depicting the extent of joint variability and dispersion of incremental costs and QALYs.

Figures 31–34 show the cost-effectiveness plane for the two for the RCT and the PPS at 12 and 24 months. In both studies, costs and QALYs are negative in the majority of samples.

Cost-effectiveness acceptability curves

A CEAC describes the probability that a treatment is cost-effective at the willingness to pay (lambda) for one QALY. Using incremental QALYs and costs obtained from the bootstrap procedure, the probability was assessed that topical ibuprofen is cost-effective compared with oral ibuprofen, for a range of lambdas between £0 and £40,000 (*Figures 35–38*).

For the 12-month follow-up, the CEACs for the RCT indicate that the probability that oral ibuprofen is cost-effective approaches 80% at a threshold of £20,000 and remains approximately at the same level for values above this threshold. In the PPS, the probability that oral ibuprofen is cost-effective is 80% at a threshold of £30,000.

For the 24-month follow-up, the CEACs for the RCT indicate that the probability that oral ibuprofen is cost-effective is 55% at a threshold of £30,000. In the PPS, the probability that oral ibuprofen is cost-effective is 80% at a threshold of £30,000.

Cost-effectiveness of topical ibuprofen, societal perspective

The main analysis of incremental costs and QALYs was repeated using a societal perspective, using

TABLE 94 *ICERs in sensitivity analyses*

	12 months		24 months	
	RCT	**PPS**	**RCT**	**PPS**
Base case (£)	8,810	2,314	15,574	Oral dominates[a]
Cost of admissions based on actual length of stay (£)	11,584	6,632	31,501	3,738
Including all prescriptions (£)	11,227	435	19,155	Oral dominates[b]
Excluding high-cost individuals (>95th percentile) (£)	9,099	2,125	16,069	Oral dominates[c]
Discount rate (6%) (£)	9,020	2,211	18,010	Oral dominates[d]

[a] Topical, +£152.08, –0.037 QALYs.
[b] Topical, +£222, –0.037 QALYs.
[c] Topical, +£167, –0.036 QALYs.
[d] Topical, +£146, –0.037 QALYs.

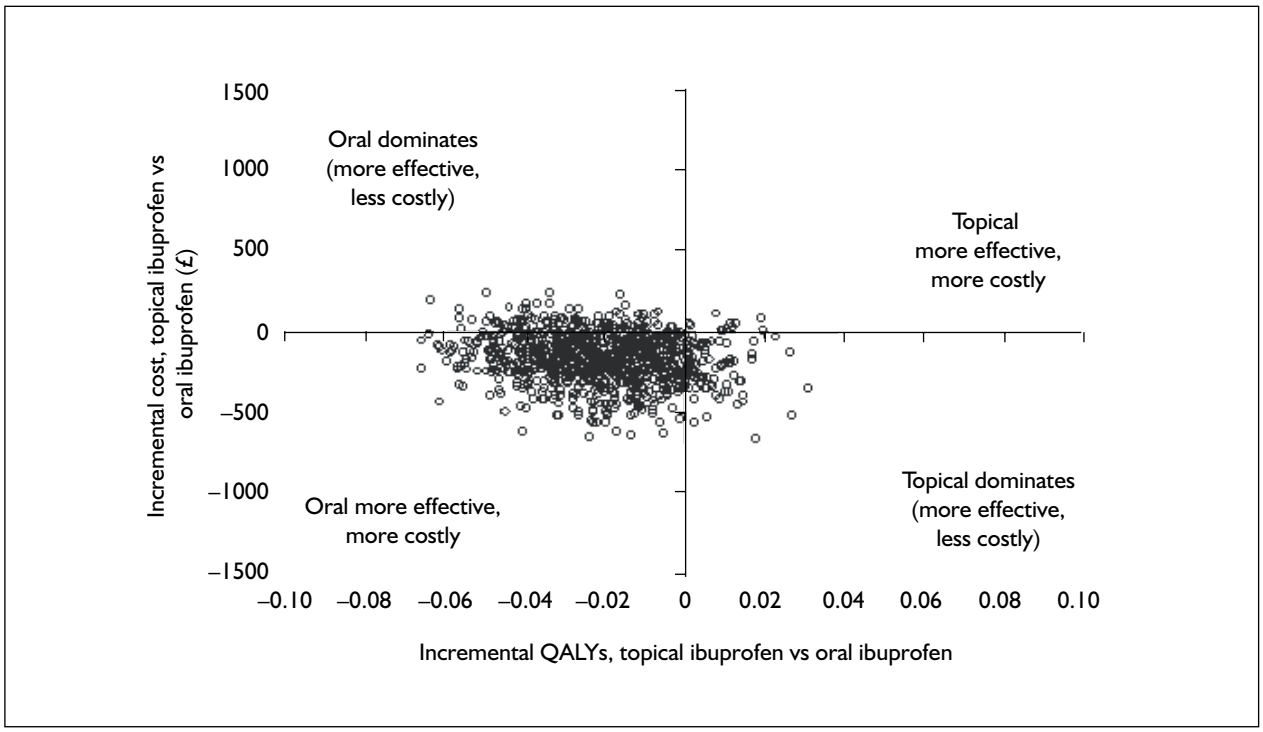


FIGURE 31 *Incremental QALYs and costs of topical compared with oral ibuprofen: cost-effectiveness planes, RCT, at 12-month follow-up*

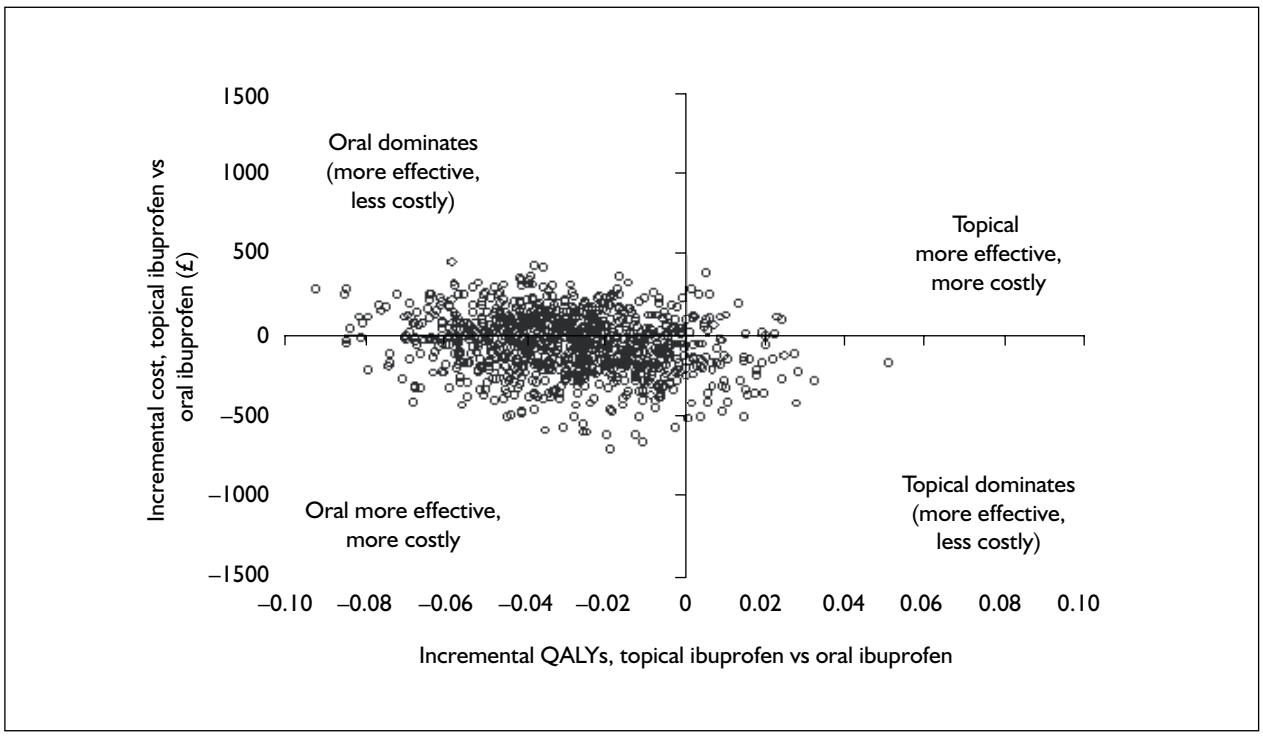


FIGURE 32 *Incremental QALYs and costs of topical compared with oral ibuprofen: cost-effectiveness planes, PPS, at 12-month follow-up*

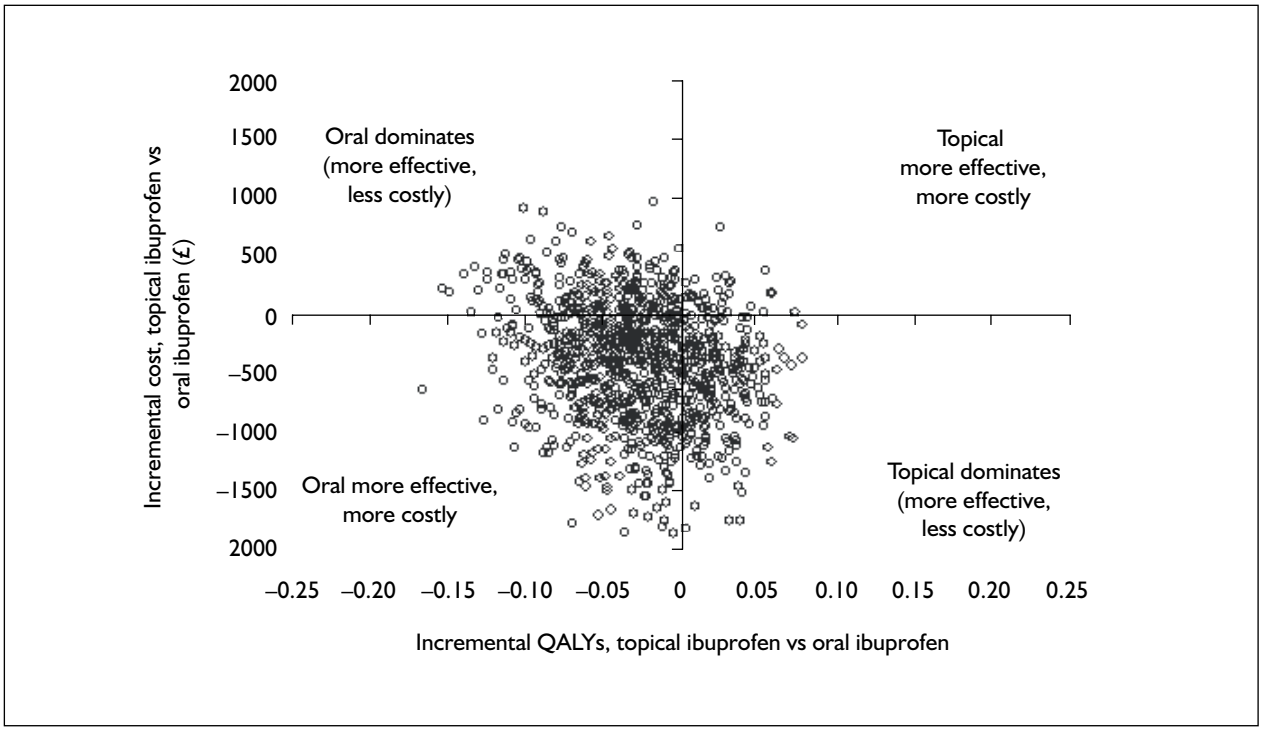


FIGURE 33 *Incremental QALYs and costs of topical compared with oral ibuprofen: cost-effectiveness planes, RCT, at 24-month follow-up*

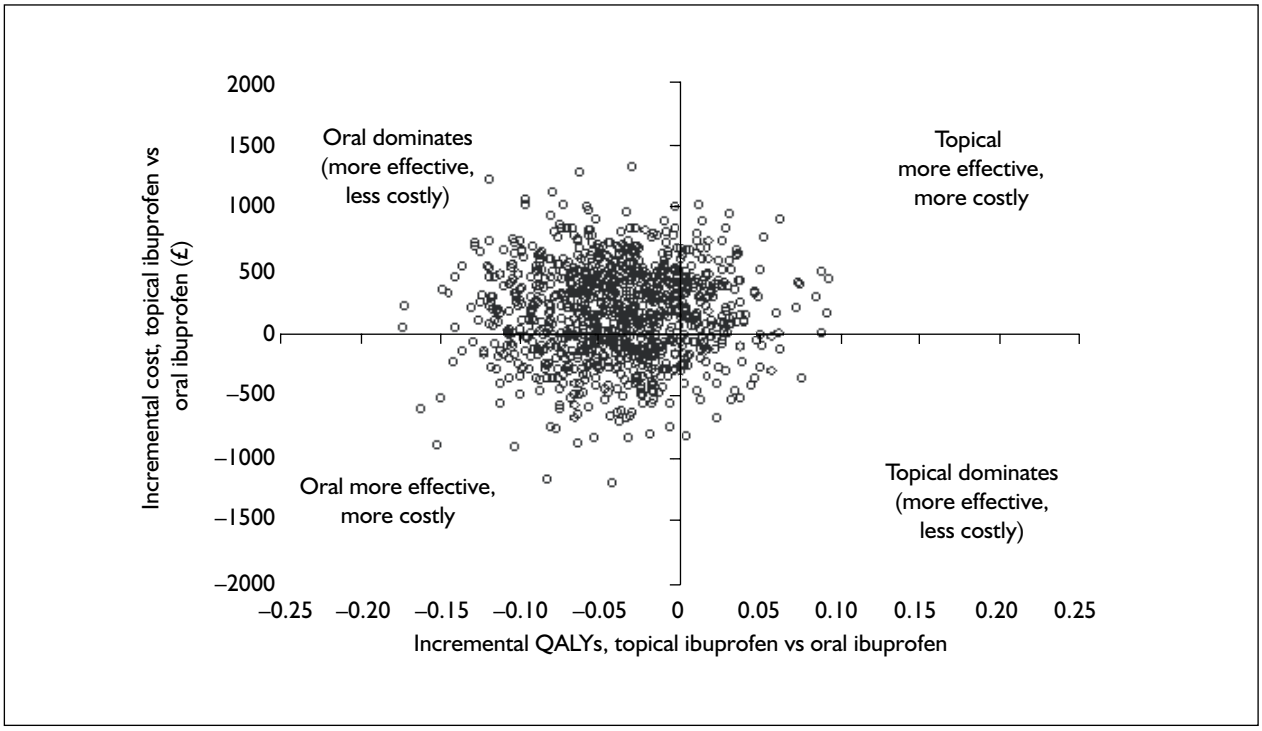


FIGURE 34 *Incremental QALYs and costs of topical compared with oral ibuprofen: cost-effectiveness planes, PPS, at 24-month follow-up*

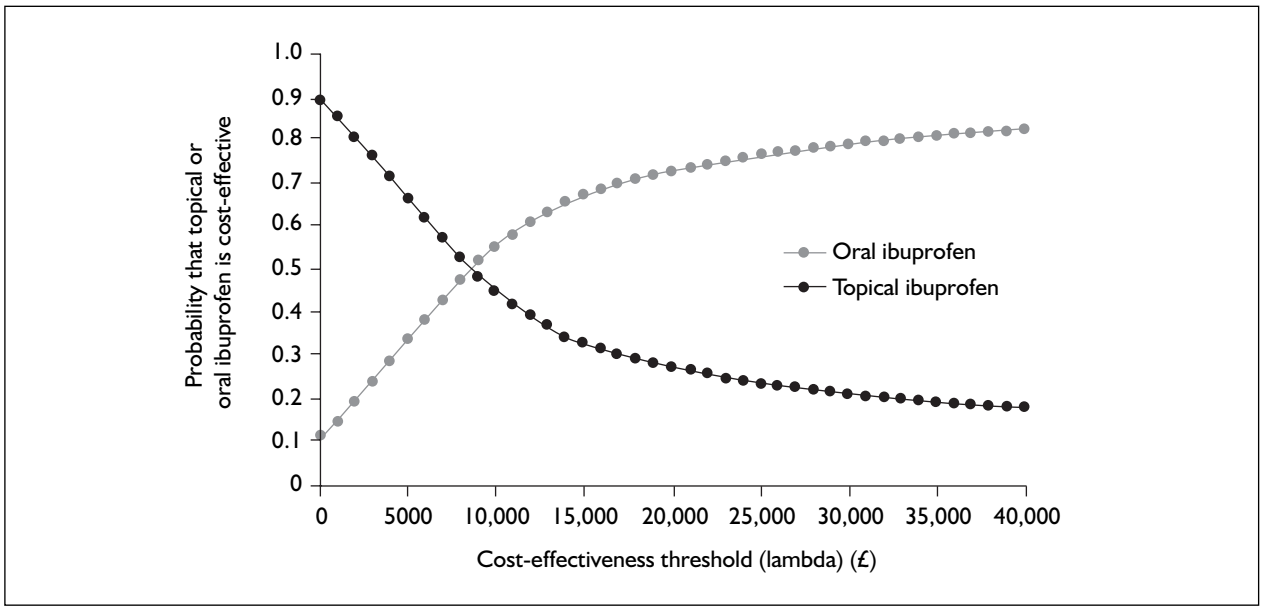


FIGURE 35 *CEACs, RCT, 12-month follow-up*

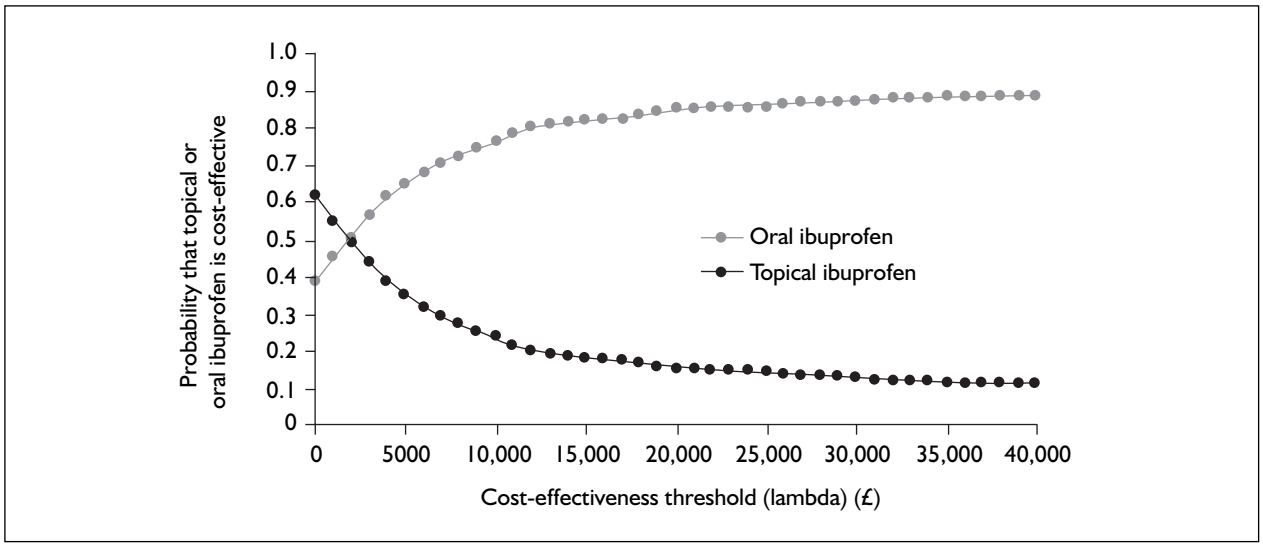


FIGURE 36 *CEACs, PPS, 12-month follow-up*

the basic, inverse weighted, regression model with no covariates for costs and adjusted for baseline utility scores for QALYs.

Total incremental costs and total incremental QALYs are presented in *Table 95*. Total costs and QALYs are rather dissimilar in the two studies, with oral administration becoming less cost-effective over the 24-month follow-up in the RCT, but being rather more cost-effective over both 12 and 24 months in the PPS.

At an ICER of £30,000, the probability that oral ibuprofen was cost-effective was around 70% over a 12-month follow-up and 50% over a 24-month follow-up. The cost-effectiveness of oral ibuprofen from the social perspective is therefore rather uncertain, particularly over the longer-term follow-up.

CEACs are presented in *Figures 39–42*.

Summary of results

Oral NSAIDs cost the NHS £191 and £72 more per participant over 1 year in the RCT and PPS, respectively. In the RCT, the cost per QALY in the oral group, from an NHS perspective, was in the range £9000–12,000. In the PPS it was £2564 over 1 year, but over 2 years the oral route was dominant, that is, both cheaper and more effective.

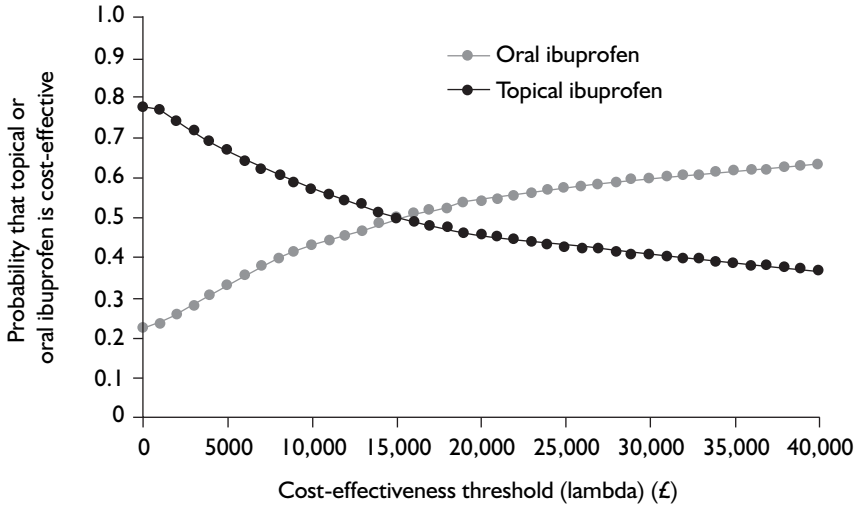


FIGURE 37 *CEACs, RCT, 24-month follow-up*

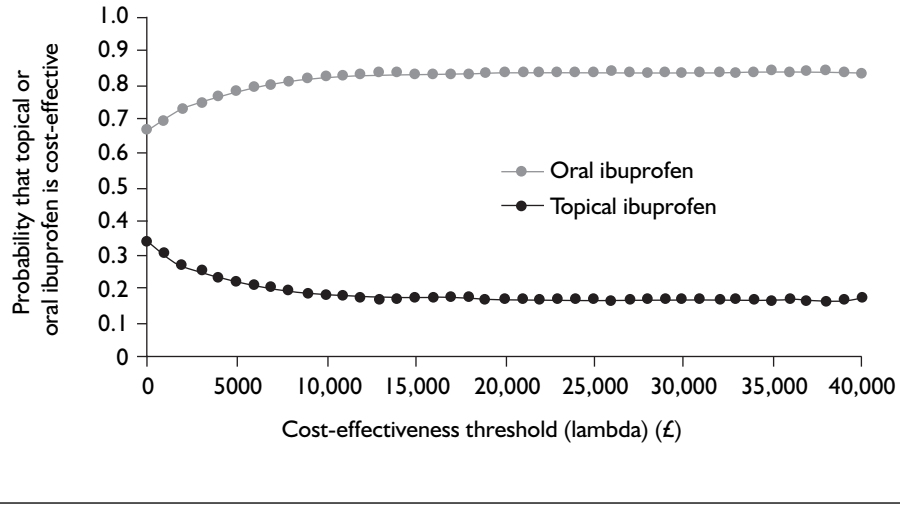


FIGURE 38 *CEACs, PPS, 24-month follow-up*

TABLE 95 *ICERs: societal perspective (incremental costs, incremental QALYs and ICERs with topical compared with oral ibuprofen)*

	RCT	PPS
At 12 months		
Incremental cost of care, topical minus oral (£)	–242.6	–148.8
Total incremental QALYs	–0.021	–0.029
ICER (£)	11,448	5,153
At 24 months		
Incremental cost of care, topical minus oral (£)	–732.5	–37.6
Total incremental QALYs	–0.027	–0.035
ICER (£)	27,235	1,066

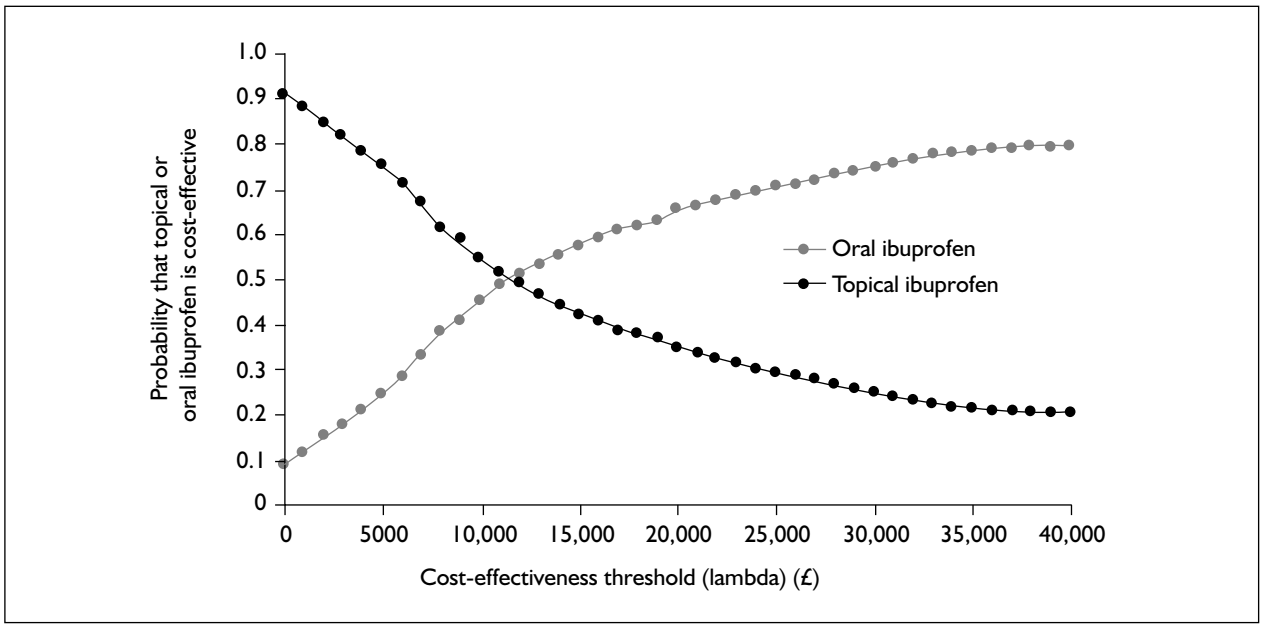


FIGURE 39 *CEACs, societal perspective, 12-month follow-up, RCT*

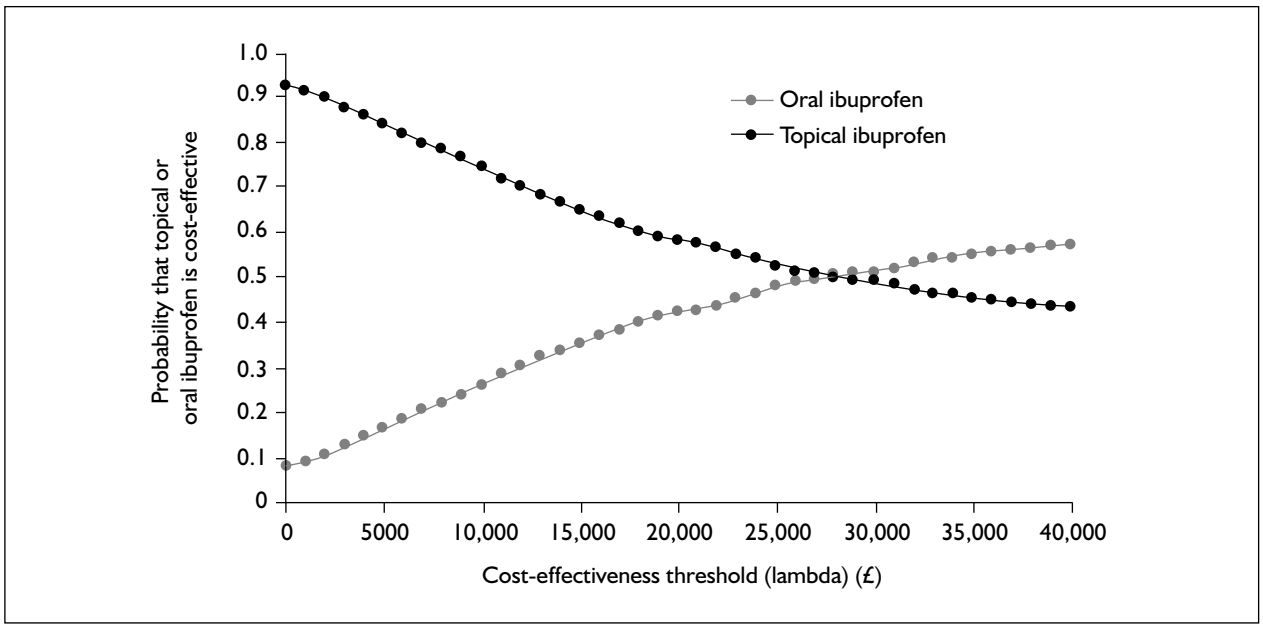


FIGURE 40 *CEACs, societal perspective, 24-month follow-up, RCT*

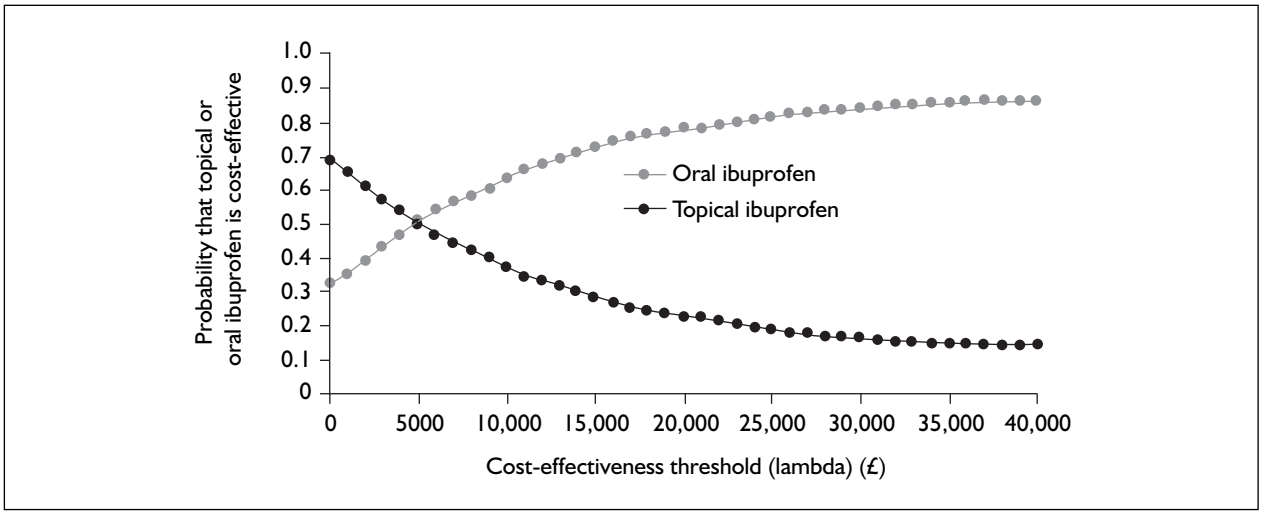


FIGURE 41 *CEAC, social perspective, 12-month follow-up, PPS*

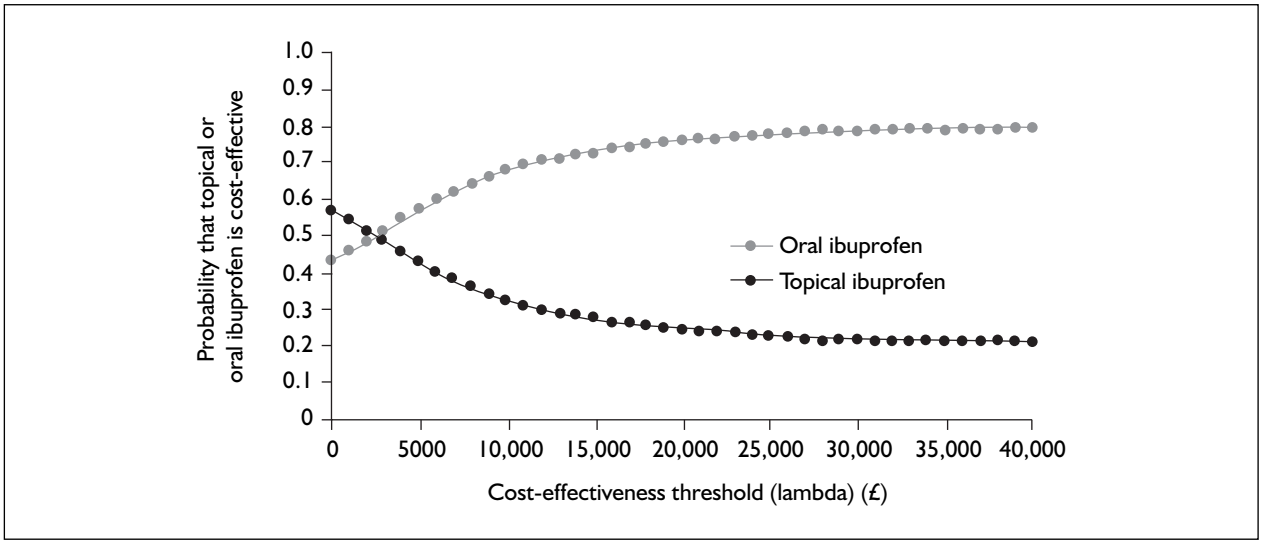


FIGURE 42 *CEAC, social perspective, 24-month follow-up, PPS*

Chapter 6

Qualitative study exploring patients' beliefs about knee pain and topical or oral ibuprofen treatment

Introduction

Decisions about care and treatment, generally, are thought to have more patient benefit if they are made jointly between the clinician and the patient[133] and if the patient trusts the physician.[134] Patient decisions about treatment often have a different grounding from those of clinicians.[135,136] For example, treatment preferences for joint replacement among the elderly are based on trading off perceived cost and benefit, disability and quality of life.[137] Factors influencing medication choices among those studied with rheumatoid arthritis were symptom relief, the occurrence of adverse effects and the availability of alternative treatments.[138,139]

Understanding the reasons and rationales for preferences is complex. Patient understanding and knowledge are built up from a variety of sources; examples include previous experience both personally and from others, unquestioned tradition, medical personnel, lay anecdotes and written material ranging from books, magazine articles and pamphlets to Internet items. Treatment preference and risk evaluation may also be influenced by the condition for which the medication is being administered and the perceived level of severity.[140]

Patient preference for particular treatments is an issue in clinical trials.[93,135] Preferences can affect outcome, recruitment, compliance, drop-out, perceived treatment effectiveness and toxicity of drugs.[141] Because these factors might have influenced both the outcome and the interpretation of the results of TOIB, a qualitative study was carried out alongside the quantitative studies. The original aim of the qualitative study was:

> 'To explore patients' beliefs about their knee pain and their expectations for treatment within the trial.'

This was modified to include the following aims:

> 'To explore patients' preferences for participating in the RCT or PPS, and treatment route; to explore patients' experiences of the minor adverse effects they had experienced from their allocated treatments and the influence of these adverse effects on their beliefs and understanding of their pain and its treatment.'

There were three elements to the qualitative study that built upon each other and overlapped in places. First some exploratory qualitative work was undertaken with participants from one pilot practice. This study was focused on general topics exploring patients' beliefs about their knee pain and its treatment. This work demonstrated the need to focus the data collection in the following two ways:

1. to sample and interview patients from both the PPS and the RCT to explore their decision-making regarding their preference for taking part in the PPS versus the RCT and choice of route of administration
2. to sample and interview patients who had experienced adverse effects during the study.

Method

Initial exploratory work

For this work, willing participants in one of the TOIB pilot practices were asked to take part in a qualitative study and be interviewed. A purposive sample informed by age, pain severity, consulting behaviour and pain location was selected. Face-to-face interviews were undertaken in patients' homes. These interviews demonstrated the importance of exploring factors influencing patients' decisions to take part in the RCT rather than the PPS, and the importance of interviewing patients who had experienced adverse effects. Quantitative data from the pilot practice used for the qualitative study were not included in the main clinical quantitative analysis. To explore the issues identified, we selected two further samples of participants from the main study, one for a qualitative study of preferences and another for a qualitative study of adverse effects. These interviews took place after the end of the main follow-up period, to ensure that the process of

being interviewed would not interfere with patients' responses to the follow-up questionnaire.

Preference study

A purposive sample of patients was selected, who had participated in either the PPS or the RCT. Sampling criteria were age, gender, trial and trial arm. The information required related specifically to their treatment choices and could be readily gathered using telephone interviews. It was acknowledged that interviewees might not accurately recall the circumstances of decisions they made some time ago, so their accounts were cross-referenced with other opinions, knowledge and behaviours.

Adverse effects study

For this work, a different purposive sample of participants was selected in either the PPS or RCT who had reported adverse effects; in some cases they had reported either stopping or changing their treatment. These interviews were undertaken after the participants concerned had completed their follow-up assessments. The interviews were conducted face-to-face, owing to the potentially sensitive nature of the content.

Participant recruitment

Participants were contacted if they had indicated on the questionnaire that they would be willing to be approached about further research. They were sent a covering letter and an information sheet describing the relevant qualitative study and what their involvement would entail, along with two copies of a consent form. One week after receiving the covering letter and information sheet they were telephoned by the relevant researcher to answer any questions about the study, determine whether they would be willing to help and, if so, to arrange a date and time for the interview. If they agreed to take part, they were asked to complete the consent forms, retain one copy for their records and return the other to the research team. The consent form asked for patients' agreement for their interview to be audio-taped, and it reiterated that any information provided would be anonymous and that interviewees were free to withdraw from the study at any time without compromising their healthcare.

Interview process

Topic guides were developed for the three sets of interviews. These consisted of a series of topics for discussion, rather than a list of structured questions. They were developed from reference to the literature in this area, brainstorming within the research team and, for the preference and adverse effects interviews, from data arising from the original exploratory interviews. *Table 96* shows the main topic areas covered by the interviews.

Data collection

A series of in-depth interviews were conducted. The researchers began by introducing themselves and reiterating both the purpose of the study and that patients might stop the interview at any time. The interviews began with general questions and moved on to more specific questions as they progressed.

All interviews were audio-taped with participants' permission and transcribed verbatim for analysis. Following transcription, interviews were anonymised, with all mention of individuals' names and places being removed.

Data analysis

The 'framework' approach was used to analyse the interview data.[142] This involved the researchers familiarising themselves with the content of the

TABLE 96 *Interview topics*

General beliefs about knee pain and its treatment	Preference interviews	Adverse effects interviews
1. Beliefs about effectiveness of drugs 2. The influence of age on beliefs 3. Being retired and attitude to medication use 4. Relationship with health professionals 5. Perceptions about health and knee pain 6. Understanding about medication and its use	1. General information about quality of life, and knee pain type and history 2. Understanding and knowledge about knee pain and medication 3. Management of knee pain 4. Motivation to participate in trial 5. Preferred treatment and why 6. Attitude to trial and treatment, including compliance 7. Attitude about the future	1. General health 2. Management of pain in the past and why 3. Expectations of treatment 4. Adverse effects experience and current beliefs about medication 5. Beliefs about the action of medication 6. Reasons for continuing or abstaining from treatment, including compliance 7. Risk tolerance

interview transcripts and then developing a thematic framework by mapping concepts articulated in the transcripts and conflating these into emergent themes. The framework was applied to the data by coding each section of text to each theme. Interview data from each theme and sub-theme was summarised in charts. One chart was developed for each major theme. These charts provided an analytical tool from which emergent concepts could be identified (see Appendix 4).

Results

Participants

Initial exploratory work

Eight patients were interviewed for the initial exploratory work, six women and two men comprising four each from the oral and topical groups. All had chronic pain of grade III or IV as measured using the chronic pain grade, and all had knee pain and pain in one or more other body locations.

Preference study

Interviews were conducted with 15 participants about preferences. Seven patients (three women and four men) were in the PPS, and eight (two women and six men) were in the RCT. Across both the RCT and PPS, patients were interviewed in all three age groups: 50s, 60s and 70 plus. Most of the interviewees in the preference study were mixed in terms of age, type of pain, medication, effect of medication and activity levels.

Adverse effects study

Interviews were conducted with 15 participants (eight women and seven men). Seven were from a topical group and eight from the oral group.

Interview findings – themes common to all datasets

Beliefs about knee pain

Mechanisms of knee pain

A common mechanism described by patients was that their pain was caused by the bones in their knee rubbing against each other because their knee bones had worn out. The knee bones were considered more likely to wear out if their knee had 'dried out', meaning that there was nothing to cushion their bones, increasing the likelihood that they would rub together and wear away.

Beliefs about pain causation and exacerbation

Knee pain underpinned patients' beliefs about cause, as nearly all of those interviewed attributed their pain to over-use and wear and tear. Some also attributed their pain to accidents and injuries that had occurred in the past and caused subsequent weaknesses in their joints.

Nature of pain

Participants described the nature of their pain in two ways: some described it as dull, nagging and present all the time, whereas others described it as a mixture of dull and nagging and occasionally sharp and intense during certain activities. These types of pain could be described as constant and transient. The nature of the pain experienced appeared to have a powerful influence on patients' decisions regarding their care seeking, the nature of treatment required and beliefs about adverse effects.

Constant pain was considered to be due to structural damage to bones and cartilage, as opposed to weakness and swelling. The level of structural damage was considered to be a result of either irreversible degeneration or of previous untreated injuries. Transient pain was linked to ideas of weakness and personal responsibility for pain, for example from over-use. Those with transient pain considered pre-emptive and reactive drug taking behaviour appropriate. *Figure 43* shows that those who are relatively active have a perception of knee pain that is less severe in degenerative terms than those who are less able and inactive.

Knowledge and understanding

Knowledge of medications

There was a wide variety of sources of information. Most knowledge was obtained via consultations and advice from those with medical knowledge. Other common sources of information were advertisements, promotional literature and articles seen in magazines and newspapers. The validity and accuracy of information, regardless of source, was rarely questioned.

Understanding of medications

There were different levels of understanding about knee pain and its treatment among those interviewed. Those who were unable to comprehend or explain the gaps in their knowledge and understanding tried to rationalise their thoughts and behaviour. For example, even though participants knew that the tablets could cause adverse effects they still took them; they often deferred the responsibility of decision-making to the GP as s/he was assumed to 'know best'. There was also a strongly held belief that because they were in a trial they would be well looked after and monitored so that nothing 'bad'

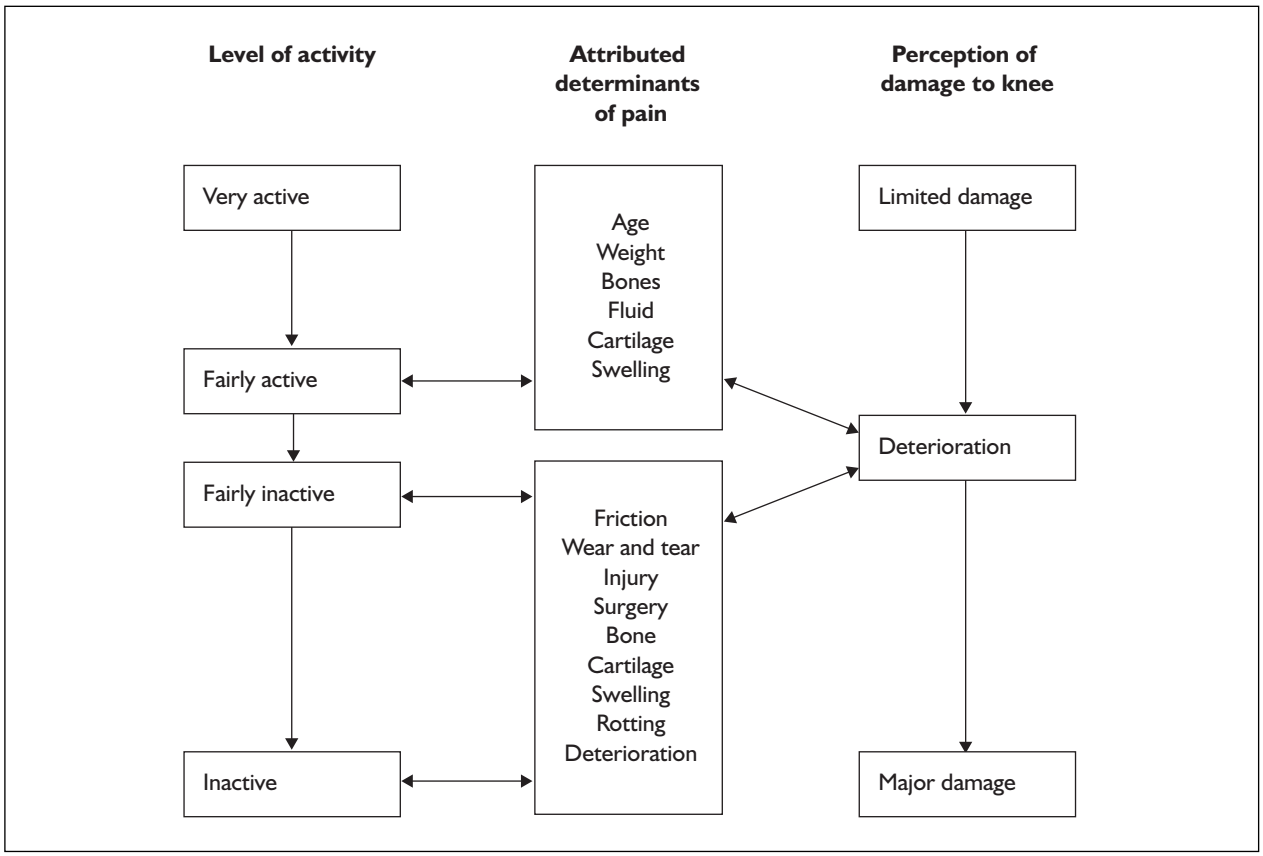


FIGURE 43 *Relationship between activity and beliefs about causes of pain and damage to the knee*

would happen. Cognitive dissonance (where behaviour and thoughts do not sit comfortably together) was evident; information about adverse effects was avoided in many cases because it increased the levels of dissonance. Deferring the responsibility of medication choice to the GP often meant that dissonance was reduced because responsibility for choice was no longer self-owned. Those who had a strong preference validated their choice as a trade-off between adverse effect and pain relief and improved function or, in the case of topical medication, a lower risk of adverse effects.

Language and suggestion

The anti-inflammatory label was rarely used by participants; there was poor understanding of the concept of inflammation or swelling causing pain. Swelling, if noticeable, was seen as a secondary condition as a consequence of the primary cause of their pain (degeneration or weakness). The common assumption was that the NSAID acted by affecting the nervous system (via local nerves or the brain).

Mechanism of action of topical preparations

Topical preparations were believed to have a localised rather than a generalised effect compared with tablets. They were thought to go through the skin to alleviate pain in the place where they were applied. The defining feature of the topical preparations was local application. The overriding beliefs were that topical preparations would not affect the rest of the body and would take effect more quickly. The visual feedback of the topical preparation disappearing into the skin, when it was absorbed into the body, was powerful; in fact, the faster it disappeared, the more effective it was thought to be. Topical preparations were assumed to have a lower dose of the active ingredients because they did not have to 'share it' with the rest of the body. Local application led to the belief that the topical preparations were less toxic to the body. Participants also believed that the act of massaging topical preparations into the skin, in addition to the active ingredient in topical preparations, helped to alleviate their pain.

Mechanism of action of tablets

Oral preparations were believed to have a generalised rather than a localised effect. Participants believed that the drug had to travel through the whole body system before it reached the knees and therefore that tablets took longer to take effect than gels. The oral preparations were

seen as toxic to everywhere but the knees. There was a contradictory belief that although the oral medication was less powerful, due to dilution, by the time it got to the knees it was still more powerful than the topical preparations. There was much confusion about how the drug got to the knee and how it 'knew' where to act. Those with multiple sites of pain were happier to take oral preparations because it might help other areas of pain while circulating around the body. Conversely, there was a perception that medication taken for a specific problem had a specific effect.

Beliefs about the effectiveness of medications
Neither route of administration was considered to be completely effective in terms of managing pain. On the whole, topical preparations were considered effective in the short term for mild-to-moderate pain and discomfort in the knees, and oral preparations in the medium-to-long term for severe pain and discomfort.

Impact of knee pain on function
This was a key issue for all patients across all three studies. Knee pain appeared to impact on functioning in one of two ways: some participants reported how their knee pain impacted on their basic functioning, that is, activities of daily living such as shopping or walking upstairs; others reported that their knee pain now stopped them from doing physical activities which they had previously enjoyed, such as skiing and running. The participants' capabilities for doing specific activities were used as markers to assess improvement or deterioration in their knee condition.

Reasons for participating in TOIB
Participants interviewed reported wanting to take part in the trial for altruistic reasons: they wanted to help the research project and ultimately other people with knee pain in the future. Some reported taking part because they wanted specific attention for their knee pain, which they felt they were not currently receiving, or because they wanted to try specific treatments for their knee pain.

The reasons for choosing treatments were complex.

Preference
Influences on preference
Participants' preferences for either topical or oral ibuprofen were based on their prior personal experiences of use, anecdotal evidence from others, their experiences of adverse effects, their beliefs about dependency and their need to feel in control of their pain management.

Some preferred the topical preparations if they had experienced adverse effects from oral preparations in the past or if they had strong beliefs about not becoming dependent on 'tablets'. Others preferred topical preparations if they were already taking many tablets for other conditions and did not want to 'add more pills to the pile'. Some reported preferring the topical preparation as they felt that it allowed them to be in control of how much medication they rubbed into their body; they were concerned about the potential for overdosing on tablets.

Oral preparations were preferred if participants were uncertain of the mode of action of the topical preparation, especially if they felt that they needed help with pain in more than one joint, or if they believed that their pain was too severe for the topical to be effective.

Figure 44 shows the issues that participants considered when choosing between oral and topical ibuprofen.

When preferences were not met, or when participants had no preference but bad experiences of taking the medication, its effect was limited or none, or the condition became worse. Generally, where preference was met patients had a positive attitude coupled with positive effects (see Appendix 4, *Table 111*).

Pattern of medication use
Differences in medication use were observed between those with constant and those with transient pain. Those with constant pain did not query taking the medication regularly because constant pain equalled constant need for medication or treatment. Those with transient pain found this concept harder to take on board. Why take a painkiller when the pain often did not warrant intervention? Those with transient pain tended to be less adherent to their chosen/allocated treatment. The advice given about medication use by trial staff and GPs varied, as this was a pragmatic trial of treatment in a primary care setting it allowed us to explore medication consumption and associated behaviour. *Figure 45* shows the relationship between the type of pain and the way in which participants used their medication.

Adverse effects of medications
Definitions of adverse effects were different between clinicians and participants. Participants' definitions could be classified as follows:

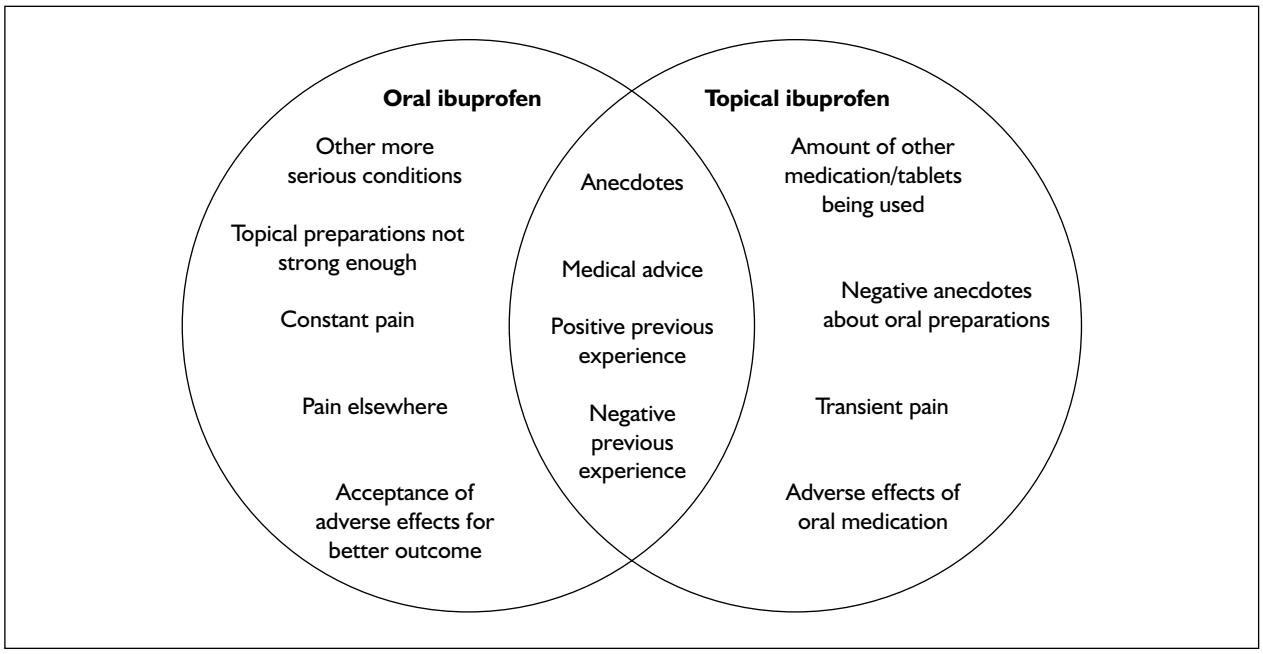


FIGURE 44 *Reasons for preferences*

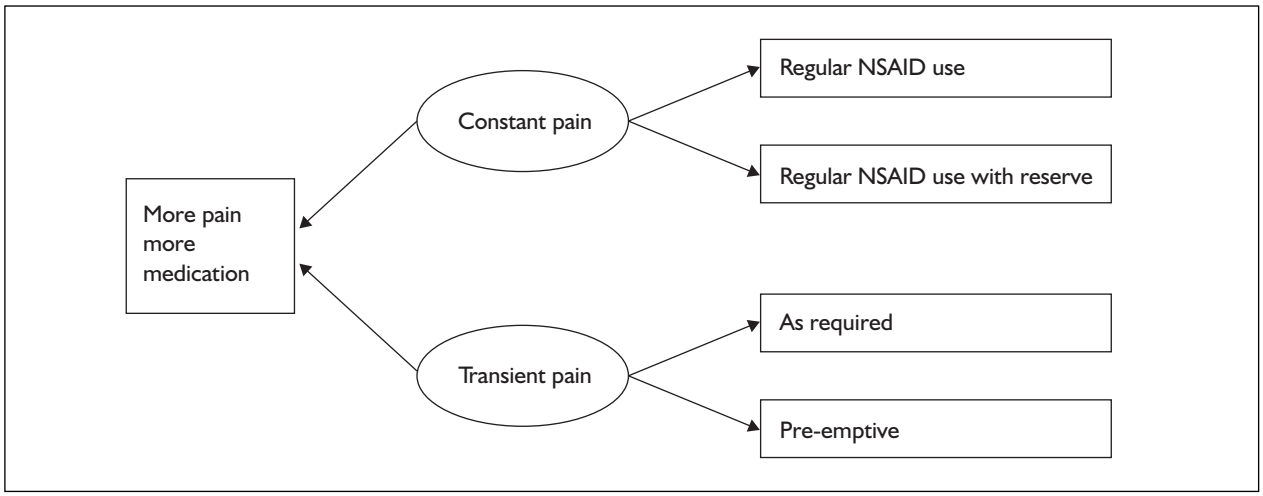


FIGURE 45 *Types of pain and medication use*

1. Noticeable reaction in the body to whatever used.
2. Any effect the medication has on the body other than the effect it had on knee pain.
3. Something that happens to the body that was not normally there.
4. Medication that interfered with the normal running of the body.
5. Medication that caused an imbalance in the system which caused a negative effect.
6. Persistent unwanted symptoms that could not be self-managed.

They used terms such as persistent, unmanageable, unpleasant or intolerable to describe adverse effects. Adverse effects from tablets were thought to be caused by:

1. the body rejecting the medication
2. tablets releasing a chemical and the body reacting to it
3. tablets entering the stomach and a reaction occurring between stomach acid and the tablet.

Nearly all of those interviewed were sceptical as to whether they could experience adverse effects from topical preparations. Since it did not work internally, patients could not understand how the topical preparations might have adverse effects in the body.

Knowledge about adverse effects
Participants appeared to have a reasonable knowledge about the potential adverse effects of NSAIDs. They believed that topical NSAIDs could cause rashes and caused fewer adverse effects because they did not enter the blood system in the same way as tablets. They were also aware that oral medications might have adverse gastric effects and, due to the publicity about adverse effects from ibuprofen, which occurred concurrently with the interviews, they also knew that another adverse effect might be heart problems.

Response on experiencing adverse effects
Some participants reported that if they experienced a serious adverse effect they would stop taking their medication and go and see their GP straight away. Others reported that they would go and see their GP only if their problem became persistent. Participants did tend to 'normalise' symptoms, by perceiving them as a consequence of 'old age'. They were very tolerant of symptoms such as indigestion, a 'sensitive stomach', constipation, diarrhoea, joint stiffness and fatigue.

Managing adverse effects by taking additional medications
Many participants reported that they would be willing to take additional medication to combat any adverse effects resulting from the ibuprofen, especially if their GP suggested it and they considered it to be a good idea. Some reported concern about taking additional medication because it might have adverse effects or interfere with the action of the ibuprofen. Participants' decision-making regarding taking additional medications to combat adverse effects was also driven by the severity of their pain and, in turn, their level of desperation to do something about it.

Provision of information regarding adverse effects
The majority of participants received information regarding adverse effects from the nurse who had recruited them into the study. Participants also reported reading the leaflet included with the medication. The main advice given by the nurse to those taking oral ibuprofen was to take them with food, and to those applying topical ibuprofen to use petroleum jelly to manage rashes. Some participants reported that they still felt that more advice on possible adverse effects and how to manage them would be useful.

Some believed that having too much information about adverse effects could be detrimental to his/her health, as it might make him/her attribute every small health problem to adverse effects, which in turn could make his/her overall health worse.

Risk–benefit of taking medications to relieve pain versus adverse effects
Participants reported that they would tolerate some adverse effects provided that the medication helped to get rid of their pain (*Figure 46*). Participants were prepared to take risks with adverse effects as long as the effect of the drug was beneficial. Because they were part of a trial and appreciated that every result was important, patients may have been more willing to suffer adverse effects even if the effect of the drug was limited, thus indicating the need to monitor trial participants closely. Mild adverse effects were considered to be a rash, an acidic stomach or a mild change to bowel habits, for example diarrhoea once per week. Participants would not tolerate adverse effects if they were continuous and if they included things such as swelling, headache, dizziness or visual problems. *Figure 46* shows the relationship between tolerance and perceived risk.

Discussion

The aim was to explore patient preference for medication and attitudes towards adverse effects. To summarise, we found that patient understanding about their pain and the action of medication was limited. Perception of severity of the knee condition was based on levels of activity, perceived irreparable damage and whether pain was constant or transient. These factors influenced medication use: those with transient pain were more likely to take medicine as and when necessary and as a pre-emptive measure; those with constant pain were more likely to use medication regularly. Factors that influenced preference were previous personal experience, experience of others, whether pain was constant or transient, the presence of pain in other areas and adverse effects.

Participants' awareness about adverse effects was greater than their understanding about their medication. Participant perceptions of minor adverse effects were different from those regarded by physicians as clinical adverse effects. Clinical adverse effects as measured by the markers in the Delphi study are often asymptomatic or tolerable to patients. Generally oral medications were seen as more powerful than topical preparations, but

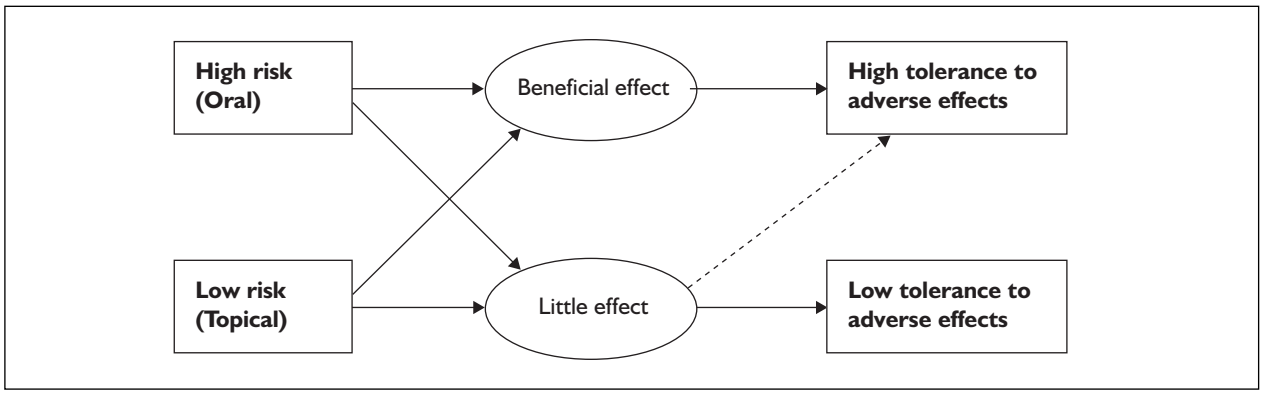


FIGURE 46 *Perception of risk and benefit*

effectiveness came at a price in the nature of adverse effects, which were acceptable if they could be tolerated or managed and curtailed in some other way.

Patient understanding about pain, the mode of action of medication and research trials is generally limited.[143–145] This has implications for preference studies and the knowledge needed for informed choice. If patient understanding is limited, how are patients making decisions about their health, their treatment and their participation in studies of this type? The ability of patients and study participants to make considered decisions in this context based on informed choice is questionable. Elderly patients, compared with younger, healthier people, are far more trusting and accepting of their GP's decisions and advice; this is thought to have an influence on their tolerance of adverse effects.[146] This, coupled with poor understanding of important adverse effects, may lead to an increase in serious adverse effects. In the elderly population, this is compounded by the increased prevalence of co-morbidities[2] and taking multiple medications. Complex treatments are thought to affect adherence and preferred treatment regimens; and not knowing to which medication an adverse effect should be attributed.[147] Our results, and the findings of others, indicate a need to monitor elderly patients closely to ensure that reported 'normalised' and 'accommodated for' adverse effects are in fact minor,[148] and that older patients are encouraged to communicate regardless of how minor they perceive their symptoms.[138]

The lack of understanding about medication caused confusion, cognitive dissonance and an inability to explain and justify decisions and behaviour. In our study, participants converted this dissonance by transferring decision-making responsibility to the GP; this translated to trusting the GP and the trial team to do and recommend the 'right' thing. Townsend and colleagues[144] observed dissonance by recognising contradictions in belief systems, such as employing regular regimens for treating one condition and flexible regimens for others, a reluctance to take drugs but an inability to be free of them and acceptance that drugs facilitate functioning but are also an admission of 'dependence' or need.

We found that when participants' preferences were met they had more positive attitudes about their type of medication. Preference was based mostly on previous experience, either directly or indirectly, medical advice and guidance and severity and persistence of pain. Previous experience narratives about beliefs for causes of pain and action of medication were either positive about effectiveness or negative about adverse effects. Knowledge was selectively routed and compiled to support individual negative or positive attitudes towards the medication. Increasing severity and persistence of knee pain affected preference; patients viewed oral preparations as more powerful than topical applications. Topical preparations were, on the whole, seen as a first point of call for managing knee pain. As severity and persistence of knee pain increased, oral preparations were preferred, followed by invasive treatment such as arthroscopy, then finally knee replacement. Adverse effects were a major determinant of preference[138,139] but patients were willing to tolerate adverse effects as a trade-off for effectiveness in pain relief and increased mobility, especially if additional treatment was available to counteract adverse effects.[138] Preference was determined by a number of factors, as already mentioned, but one factor that was not apparent in our study, but relevant to elderly patients considering total joint replacement, was the level of social support

available to them.[137] Interestingly, this consideration was not deemed important when contemplating participation in this trial for ibuprofen, indicating that the level of risk and consequence was different to that perceived for knee replacement surgery.

Previous research has indicated that increasing patient knowledge through education about the causes of knee pain, mode of action of medication and adverse effects improves both compliance and informed choice.[143,149] We found that participant comprehension was dependent on the use of lay terminology and effective face-to-face communication. Few participants read and remembered written instructions and many actively avoided reading about adverse effects for fear of experiencing them through the power of suggestion.

Adverse effects considered important by clinicians were different from those considered important by patients. In our Delphi study, we focused on adverse effects such as low serum ferritin or raised creatinine levels, hypertension and indigestion that may lead to stopping NSAIDs. Patients however, regarded headaches, dizziness, nausea and increasing knee pain as adverse effects. These are more likely to manifest themselves as conditions that affect lifestyle and function. The clinical measures can be asymptomatic and the patient may be unaware of them. There was generally a high tolerance level to adverse effects and a tendency to normalise general malaise, aches and lack of well-being as resulting from 'being old'. Benson and Britten reported a balancing strategy between drug effectiveness, preference and unwelcome and acceptable adverse effects with anti-hypertensive drugs. Where unwelcome adverse effects were experienced, they were tolerated better when other managing strategies/drugs could counter them.[148] This had resonance with our findings. Adverse effects were defined in our population as persistent,

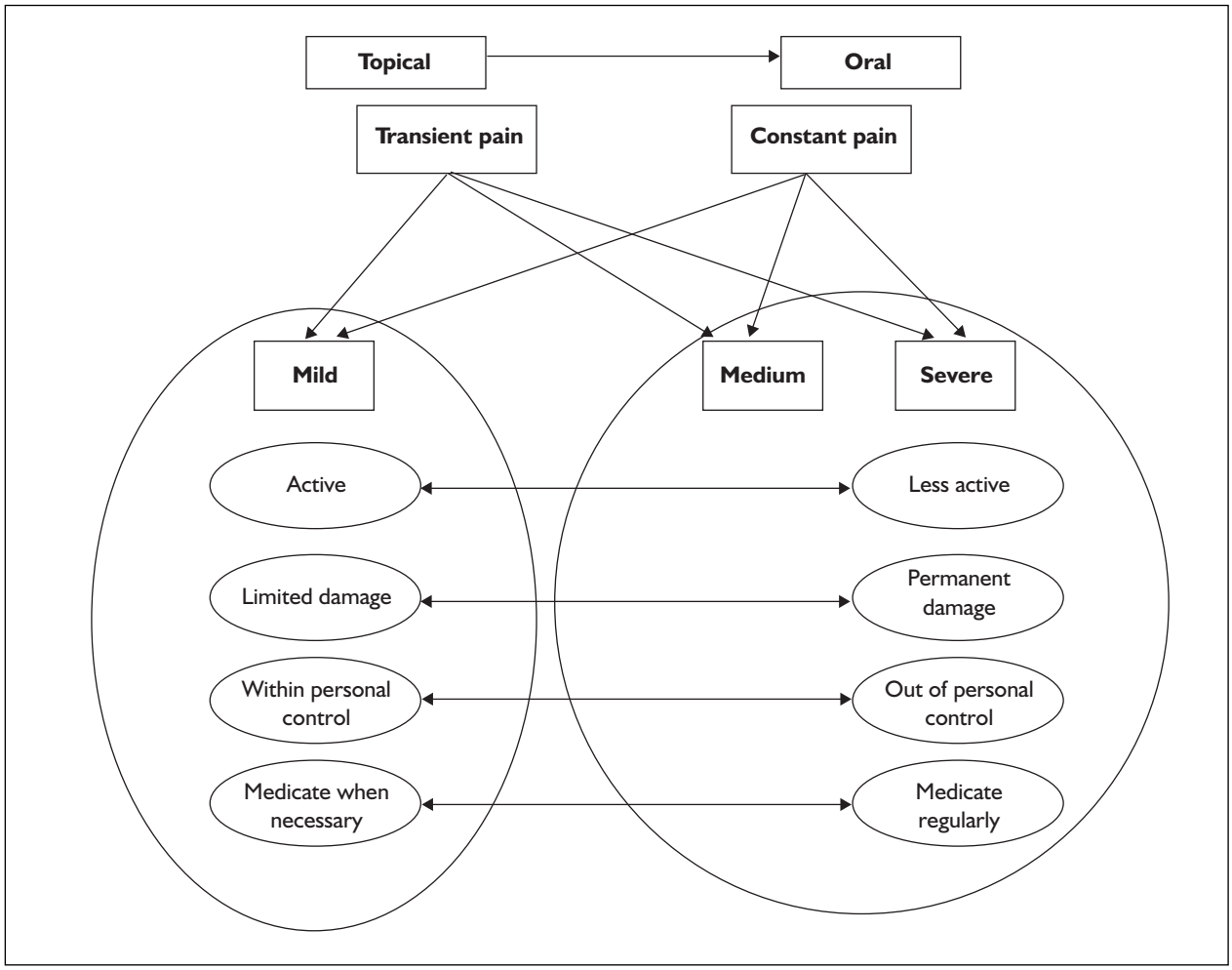


FIGURE 47 *Relationship between ibuprofen preparation, type of pain and perception of pain and damage*

unmanageable, unreasonably self-managed, unpleasant or intolerable.

Adverse effects informed preference and influenced adherence to medication use. Patients determined their own treatment protocols based on effectiveness of the drug, the degree of tolerance to the adverse effect, pain elsewhere and the presence of other more serious conditions. There were four types of drug-taking behaviour noted in our study: regular; regular low dose with room for extra as and when required; when required; and pre-emptive. These were influenced by the nature of pain, the intensity of pain and the level of adverse effect (*Figure 47*).

Overall, medication choice and use were determined by perception or experience of adverse effects, the presence of other conditions and consumption of other drugs, the type of pain (constant or transient), pain severity, levels of activity and perceived level of damage (see *Figure 47*). The presence of transient, less severe knee pain was linked to topical preparation choice, which was perceived as the less potent and risky medication route. More severe, constant pain warranted a more potent intervention, which was perceived as oral medication. The only exception to this was when participants were taking other medication for illnesses which were regarded as more serious; therefore, their knee pain was not a priority and was seen as less severe – even though it may have been bad, it was not life-threatening. *Figure 47* summarises this relationship.

During the course of this study, there were two occasions when concerns about NSAID-related adverse effects were widely reported in the general media. This affected the attitudes of patients and influenced their perception about their medication. The second of these, on the potential cardiovascular risk from ibuprofen,[53] occurred during the interview study, and enabled us to explore patient understanding of adverse effects in more detail.

Conclusions

Lack of understanding about knee pain and the action of medication can lead to increased tolerance of symptoms. Elderly patients tend to normalise and disregard the existence of minor adverse effects. These may then go unattended and the patient may consequently and inadvertently increase his/her risk of serious adverse effects.

Increasing patient understanding by face-to-face discussion, rather than written information, may improve adherence, acceptance, perception of effectiveness and informed choice. Communication via consultations allows practitioners to listen to their patients' needs and prescribe preparations that are practical, appropriate, suitable and acceptable to the patient.

Chapter 7
Discussion

Key findings

Primary outcome measure

Our primary outcome measure was the difference in the global WOMAC change score at 12 months. This outcome was equivalent between oral and topical groups in both the RCT and PPS: topical – oral. The RCT difference = 2 (95% CI –2 to 6), PPS difference = 1 (95% CI –4 to 6). There was a difference, of borderline statistical significance, in the WOMAC pain score in the RCT at 24 months and end of study. All but one of the differences between oral and topical groups in the WOMAC subscales were within the bounds set for our definition of clinical equivalence. The exception was pain at 24 months, where smaller numbers meant that there was a wide CI, making it difficult to demonstrate equivalence. Overall these data show that advising patients to use either oral or topical NSAIDs produces equivalent clinical knee pain outcomes. Our data do not tell us whether this is because the approaches are equally effective, or equally ineffective. Support for the notion that neither is effective is given by the absence of improvement in pain scores between baseline and follow-up.

There are problems interpreting any within-group differences because the majority of the participants had been using NSAIDs, topical or oral, in the previous year. Although we asked the participants to avoid them prior to the baseline assessment, they may have been using these or other analgesics. However, we are satisfied that substituting either an oral or a topical NSAID for current treatment produces equivalent knee pain outcomes.

Secondary outcome measures

Major adverse effects

There were no significant differences between the oral and topical groups in either study in the proportion or rates of major adverse effects (deaths or unplanned hospital admissions). Two deaths occurred during follow-up: one from prostate cancer and one from a subarachnoid haemorrhage, both in the PPS topical group. Neither of these is likely to be directly related to NSAID use.

This death rate is substantially less than would be expected in the general population of this age. In 2004, the mortality rate in people aged over 50 years in England and Wales was 28 per 1000 person-years (http://www.statistics.gov.uk/downloads/theme_health/Dh2_31/DH2No31.pdf, accessed 4 December 2006). This means that if our participants were representative of this age group we might have expected up to 16 deaths amongst our 585 participants. We identified only one participant who had an upper gastrointestinal haemorrhage, which occurred while the patient was in hospital awaiting a hip replacement: this participant was taking oral ibuprofen and was advised to discontinue it. An observational study of NSAID users, with a mean age of 63 years, found a crude rate of upper gastrointestinal haemorrhage of 18 per 1000 person-years.[150] These figures suggest that around four upper gastrointestinal haemorrhages per year might have been expected in those taking oral NSAIDs. Similarly, there were comparatively few unplanned admissions amongst our participants. Hospital Episode Statistics suggest that around 13% of those aged over 45 years have an unplanned hospital admission each year (http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=202, accessed 4 December 2006). Thus, around 76 of the participants might have been expected to have had an unplanned hospital admission; in fact, only 33 did so.

Although there were no differences in major adverse events between the topical and oral groups, the number of events was too small to draw any conclusions and was substantially smaller than the number expected in the general population of this age. The TOIB trial was not designed to try and show a difference in serious adverse events and the serious adverse event data suggest that we recruited participants who were substantially fitter and more tolerant of NSAID-related adverse events than their peers. Recruiting prevalent rather than incident cases makes it more likely that those who have already had adverse effects from oral ibuprofen would not be eligible for the study.

Minor adverse effects

Definition of minor adverse effects

Using the Delphi technique in an expert group of GPs with an interest in rheumatology, we were able

to define and describe the adverse effect profile of NSAIDs in the study participants in considerable detail. The specified minor adverse effects may be useful for future studies of NSAIDs.

Minor adverse effects

Some significant differences were found in adverse effect rates between the two groups in the RCT, but not in the PPS. It was also found in the participant self-report that substantially more people in the RCT oral group stopped their medication because of adverse effects than in any of the other groups. These observations may indicate that those people who joined the oral group in the PPS had preselected themselves because they were tolerant of NSAID-related adverse effects. Those in the topical group had possibly selected themselves because they were intolerant of oral NSAIDs.

A small excess of minor respiratory adverse effects was found in the RCT oral group, but this did not translate into an overall difference in defined adverse effects. Interestingly, although more of the RCT oral group had a 15% or larger reduction in PEF, which is generally accepted as clinically important, there were only three new diagnoses of asthma, and there were no reported increases or changes in asthma treatment. Additionally, renal function as measured by serum creatinine was found to deteriorate more in the oral group in the RCT. There are few long-term data on the relationship between changes in creatinine and adverse patient outcomes, but a number of inpatient studies have shown a linear relationship between increasing creatinine and adverse outcomes.[151] In one study of women with established cardiovascular disease, a serum creatinine of over 124 mmol/l was a strong predictor for fatal and non-fatal myocardial infarction. Deteriorating renal function was not found to increase the incidence of adverse cardiovascular events in the long term.[152] There are, however, grounds for concern that the difference that we found in serum creatinine, although small at an individual patient level, could have a large impact at a population level. No differences were found in gastrointestinal adverse effects. These findings suggest that the importance of renovascular and respiratory NSAID-related adverse effects, which may have few overt symptoms, is not being adequately recognised.

Although not conclusive, there is a suggestion here that there is an excess of some minor adverse effects in those randomised to the oral group. In our original sample size estimations we estimated that we would have sufficient statistical power to show a difference in the proportion with minor adverse effects of 30 and 50%: none were shown. The similarities in minor adverse effect rates may indicate how fit the participants were, or that many of those randomised to oral NSAIDs had stopped taking them at the end of 12 months, thus reducing the possibility that any changes could be demonstrated at the 12-month assessment. Whatever the explanation for the findings, there is ample evidence, external to this study, of the overall risks associated with oral NSAID use.

Other secondary outcomes

There were few differences in the other measures of pain and function. Some participants might have gained more overall benefits from oral NSAIDs. In the RCT, substantially more participants reported that they had stopped their topical preparation because of lack of effect, although the prescribing data suggest that similar proportions (approximately 25%) were still using as much of the originally prescribed treatment as other drugs in the fourth quarter of follow-up. Those in the oral group were more likely to have a reduction on the chronic pain grade, a measure of overall pain, at 3 months and end of study; this group also had a small and marginally significant increase in satisfaction with treatment. This suggests that although the knee pain outcomes were equivalent, those allocated to oral medication might have derived benefits in overall pain and disability owing to the systemic effects of oral NSAIDs.

Economic evaluation

There was very little difference in the utility scores between oral and topical groups in either arm of the study. In the RCT, NHS costs were lower for the topical group despite the higher cost of the study drug. This was partly due to expenditure on cardiovascular and gastrointestinal drugs in the oral group. Although information was collected on prescribing during the study, no information was collected on drug use prior to study entry, so we cannot be sure that these differences were not present prior to study entry. The primary analysis for cost-effectiveness was based on the 12-month data. There were substantial differences in the economic analyses between the PPS and the RCT. Although the PPS findings are of interest and can inform our views on the choice of treatments for those who prefer oral or topical medications, it is the RCT data that should be given the greatest weight. These show that advice to use oral preparations is both more costly and more

effective than advice to use topical preparations. From an NHS perspective, using the RCT data, advice to use oral preparations is cost-effective if purchasers are prepared to pay £8600–9100 per QALY over 12 months and £12,000–18,000 per QALY over 24 months; below this value topical treatment is more likely to be cost-effective. There is an 80% likelihood over 12 months and a 55% likelihood over 24 months that oral NSAIDs are a cost-effective choice with a willingness to pay £30,000 per QALY. From a societal perspective, in the RCT, the cost per QALY is £11,500 at 12 months and £27,000 after 24 months.

A plausible explanation for the apparent contradiction between the analysis of the clinical data demonstrating equivalence in knee pain outcomes and the health economic results showing improved health utility is that oral NSAIDs are having greater effects on pain elsewhere in the body. Since we are likely to have underestimated the incidence of serious adverse effect rates, we may have underestimated the increased costs and overestimated the QALY gains in the oral group. For example, Segal and colleagues estimated that, when considering major adverse effects of treatment, when compared with placebo, oral NSAIDs brought about a loss of between 0.029 and 0.044 QALYs.[153] Additional unmeasured effects of this order of magnitude would make oral medication appear substantially less cost-effective.

It seems unlikely, based on the RCT data, that the use of oral NSAIDs can be recommended on cost-effectiveness grounds alone. In the PPS at 24 months, from an NHS perspective, oral treatment dominates topical, that is, it is cheaper, more effective and more likely to be cost-effective at all levels of willingness to pay. From a societal perspective, the cost per additional QALY from advising oral medication, in the PPS is £5000 after 12 months and £1066 over 24 months.

This results in an interesting conundrum. Based on the 24-month PPS data, there appears to be a cost-effectiveness argument for not using topical NSAIDs for older people with knee pain who would prefer to use them. The results of the cost-effectiveness analysis in the PPS have been driven both by the effects of the medications and by the baseline characteristics of the participants. If, as seems likely, those who preferred to be in the topical group were generally less fit than those in the oral group, then the cost savings and QALY gains could be just a function of participants' overall health state, even though we, at least partially, controlled for this by adjusting for baseline QALYs in our analysis. It is likely that the minority of the PPS cohort who selected oral ibuprofen are a highly self-selected group who tolerate oral NSAIDs well. The observed difference may be just the increased healthcare costs required to keep those in the PPS topical group who are slightly less fit up to the same level of health utility. Hence there is no cost-effectiveness argument for denying oral NSAIDs to those older people with knee pain who wish to use them.

Use of prescribed medication

In all groups except the PPS oral group, there was some crossover between routes of administration. When the topical groups also used oral NSAIDs, these were likely to be something other than ibuprofen. In all groups, the amount of ibuprofen and other NSAIDs prescribed diminished over time, but less so in the PPS than in the RCT. Although the prescribing data indicated good adherence in the first 3 months of the study, during months 9–12 only a minority of participants in the RCT oral group received prescriptions for NSAIDs by their allocated route (46% in the oral group, 29% in the topical group). Very few in the oral group changed to topical treatment but 23% of those in the topical group had been prescribed an oral NSAID. As a result, during months 9–12, those in the oral group were prescribed an average of 24 DDDs of oral NSAID and those in the topical group RCT were prescribed 16 DDDs. This convergence in average use is at least partly explained by participants' reported reasons for changing medication. In the oral group they changed because of adverse effects and in the topical group they changed because of poor clinical effect. The topical group appeared to be in more pain than the oral group when they changed treatment type.

The findings are indicative of likely NSAID use, but the actual amount consumed may be different due to failure to have prescriptions dispensed, failure to take dispensed medication, use of existing supplies of medication and use of over-the-counter preparations. By the end of 12 months, many participants were using comparatively little medication for their knee pain. Adherence was much better in the PPS but clinical effects were again equivalent. This finding, and the equivalence in clinical outcomes found in the early stages of the RCT when adherence was good, give us additional reassurance that clinical effects are equivalent.

There were few significant relationships between drug use (from prescription data) and adverse

effects. There were some weak relationships between WOMAC scores and adverse effects. No adverse effects were associated with higher WOMAC scores and the increased use of a specific drug. Without knowing how drug use actually affects the WOMAC score, it is not possible to decide if the relationships between WOMAC scores and adverse effects are mediated through drug use or not.

The level of adherence in this study contrasts with that achieved in some other studies of NSAIDs; for example, in the VIGOR study, 71% of participants continued medication during follow-up, 99% of whom took at least 75% of the doses intended.[110] The higher drug doses used in many studies and the better adherence rates mean that the adverse effect rates observed in some other trials may overestimate the likely adverse effect rate when these drugs are used in routine practice.

The pattern of drug use that was observed is more representative of how older people use NSAIDs in normal circumstances, rather than strict regimens applied in other RCTs. This fits with the findings from our qualitative work, which indicated that older people with knee pain make logical choices about when to use their medication according to the health impact of their knee pain. The conclusion that GP advice to use oral or topical NSAIDs for knee pain produces equivalent clinical outcomes appears robust.

Other drug costs, particularly cardiovascular drugs, were higher in the oral group in the RCT. Use of non-NSAID analgesia was similar in all groups.

Risk–benefit analysis

There was a linear relationship between having a poor WOMAC score over a period and an increased risk of some adverse effects and outcomes. This could be because pain and difficulty moving affect the outcomes directly or indirectly through a change in behaviour such as reduced exercise and/or worse diet. Alternatively, it could be because those in more pain tend to take more painkilling drugs, some of which have adverse effects. If the added risk and added benefit are considered over the year, in patients who may have had problems and been taking medication for some time, then there is much less evidence that the added risks and added benefits are associated. If the topical PPS is excluded where there was no relationship, an increase in WOMAC score is only associated with an increase in ferritin levels, presumably good, and a decrease in FEV_1, which is bad. Neither effect is large or highly significant.

Effect of preferences

An important part of this study was to consider the effect of patient preferences on the outcome of treatment. Patient preference studies have been used to explore the effect of preferences on treatment outcomes in other areas, such as early pregnancy diagnosis and termination of pregnancy.[154,155] In the study, the preference study group differed in a number of baseline features from the randomised group. They tended to be older, have a lower occupational class and have more troublesome pain in other parts of the body. Clinical outcomes were similar, but adherence and cost-effectiveness differed markedly between the RCT and PPS. A systematic review of the measurement of preferences in RCTs suggested that there was little evidence that the characteristics of those who agreed to be randomised differed from those who did not; this is in contrast to the results from our study.[93] This meant that it was not possible to combine the groups for comparison, as has been done in some other studies using a similar design.[156] Another factor making comparison difficult is that early in recruitment a large majority of participants chose the PPS, meaning that additional practices had to be recruited later to enter participants into the RCT only. This made the follow-up time longer for the PPS than the RCT, and it also meant that, in respect of the additional practices, some participants were likely to have been excluded because they were unwilling to be randomised, whereas other will have been included in the RCT who would have chosen the PPS if given that option. It seems that many people made choices based on prior experience of NSAID medication and tended to choose the alternative to the route they had most recently used. Topical was overwhelmingly the preferred route in the preference arm; this concurs with the anecdotal experience of GPs. The group in the PPS who chose oral medication was small, so inferences must be cautious. In the PPS, in contrast to the findings in the RCT, oral ibuprofen was not associated with an increase in adverse effects, it was less costly and had a small positive effect in health utility. This may reflect the participants' previous good experience with oral NSAIDs.

Qualitative study

Participants' choice of preparation was based on a number of factors, such as previous experience of

oral medication (including adverse effects), other illness, pain elsewhere, anecdotal stories, convenience, severity of pain and perceived degree of degeneration, which was closely aligned with level of activity. Lack of understanding about knee pain and the action of medication led to increased tolerance of symptoms. The participants tended to normalise the presence of 'minor adverse effects', symptoms such as indigestion and sensitive stomachs as due to the effects of age. However, if these potentially important symptoms are disregarded, patients may inadvertently increase their risk of serious adverse effects.

Participants' understanding of the action of their medication and reasons for their pain or condition was generally poor. Increased understanding may improve adherence, acceptance, perception of effectiveness and informed choice. Patients were more receptive to verbal communication: face-to-face consultations allow practitioners to listen to their patients' needs, explore 'normalised' symptoms in more detail, acknowledge preferences and prescribe preparations that are practical and appropriate to the patient's condition and lifestyle.

Strengths and potential weaknesses of the study

Generalisability

Participants were drawn from a nationally representative group of practices. The mean Index of Multiple Deprivation score for our study practices was slightly higher than the national average, and the proportion of non-white ethnic groups was lower than the national average. We assumed that the routine care provided by these practices is likely to be similar to that provided elsewhere in UK general practices.

The selection process produced a sample of older people with knee pain who were younger and generally fitter than those identified in our computer searches. This has consequences for the interpretation of the adverse effect data. There are good reasons to believe that recruited participants are less likely to suffer NSAID-related adverse effects compared with the general population of NSAID users (see 'Secondary outcome measures', p. 107). If the selection process identified participants whose comparative response to topical and oral NSAIDs was different to the general population, there are potential problems interpreting the effectiveness results. We are aware of one primary care observational study which found that those with more severe impairment of health-related quality of life and a shorter history of OA gain greater benefit from oral NSAIDs,[157] and another short-term trial looking at predictors of drug responsiveness to treatment with ibuprofen or paracetamol: it did not find that severity predicted treatment response.[158] We are unaware of any studies predicting response to topical NSAIDs.

If impaired health-related quality of life and longer duration truly indicate a lower possibility of a benefit from oral NSAIDs, then the relatively fit older population may be less likely to gain a benefit from these compared with the other older people consulting their GP. However, in the absence of data on predictors of treatment response to topical NSAIDs, this possibility should not affect the interpretation of our results.

The participants were all identified by contact with their general practice for treatment of their knee pain. They may not be directly comparable to those who self-manage their knee pain, but over 97% of our participants met the ACR clinical criteria for knee OA. They appeared to have similar levels of pain and disability to participants in other primary care-based intervention studies and studies of those consulting their GP for OA.[159,160] We conclude that the results are at least as applicable to routine general practice as the current literature.

CONSORT statement for equivalence studies

An extension to the CONSORT guidelines, dealing with equivalence and non-inferiority trials, was published in 2006, after the start of our study.[161] The guidelines recommended that study design, study populations, dosage and outcome measures should be the same as those used for efficacy studies on a comparator drug. There is not a suitable comparable trial of either the intervention or advice to use topical or oral NSAIDs. The efficacy studies for oral ibuprofen took place decades ago, when outcome measures in common use were different to today. We used the WOMAC questionnaire, which is a well-established measure of outcome in studies of knee OA. In addition, there is a short-term study showing that oral ibuprofen given at 1200 mg daily in a primary care population with hip and knee OA is superior to paracetamol.[124] This indirect evidence gives some support to the notion that the population, dosage and outcome measures that we used are reasonable.

Applicability to routine practice

Our results address the pragmatic question, 'does advice to use oral or topical NSAIDs produce equivalent knee pain outcomes?'. We have not sought to address the more explanatory question, 'are the effects of oral and topical NSAIDs equivalent?'. A different study design would be needed to address this latter question; the former is more relevant to routine practice. Although our selection procedures meant that our study population was not entirely representative of all knee pain sufferers presenting to primary care, they were all patients who were receiving care from their GP for knee pain, and for whom the GP would have considered prescribing NSAIDs if the study were not taking place. In practice, the choice of treatment is not random, it is affected by both clinician and patient preferences. The preference study arm increases the relevance of our findings to routine practice.

Recruitment

Recruitment to the study took longer than expected. Several factors contributed to this. First, technical difficulties were encountered in searching the general practice records for potential participants and sending the initial approach letters. Second, delays were experienced in obtaining local research ethics approval in some areas and, during the recruitment period new regulations on research governance were introduced. Separate requests for approval were required in each area for practices starting recruitment after the change in regulation. Third, a larger than expected proportion of potential participants were excluded from the study due the safety criteria. Finally, in practices offering a choice between the RCT and the PPS, a larger than expected number of participants chose the latter. We eventually met our calculated sample size for the RCT by recruiting additional practices to offer the randomised study only. We did not meet the required sample size for the PPS. Follow-up rates were higher than expected and the completeness of the data was good, meaning we had ample statistical power. The slow recruitment meant that many participants failed to achieve 24 months of follow-up, particularly in the RCT. This reduced the power of the 24-month analysis in the RCT and made comparison of the RCT and PPS more difficult.

We attempted to select practices that were representative of the UK as a whole but we were only partially successful. Our practices were spread across the UK but tended to be in small towns or suburbs rather than in inner city areas. Only 1% of participants belonged to a non-white ethnic group, compared with the UK average of 7%. This may be because our practices did not have a high proportion of patients belonging to ethnic minorities. The non-white UK population is concentrated in London (46%) and in the West Midlands (14%); unless these areas are specifically targeted, it is difficult to recruit participants from ethnic minorities in studies of the general population. It is also possible that older people from ethnic minorities may be less willing to participate in research or be less fluent in English. In addition, where ethnic minority populations exist, they may contain a smaller proportion of older people than the population as a whole. In the UK in 2000, 19% of the non-white population were aged 45 years or over, compared with 40% of the white population (http://www.statistics.gov.uk/lib2000/section192.html, accessed 4 December 2006).

As mentioned previously, our participants may differ from patients presenting in general practice in two important and related areas. First, although we had no upper age limit for recruitment, there was a preponderance of participants from younger age groups. This may not be typical of patients seeking care for knee pain, whom one might expect to be older. It is of note that the prevalence of troublesome knee pain tends to fall in the very elderly, suggesting that they may be normalising their pain and disability and be less likely to seek GP care for it. Second, although the majority of our participants were identified because they were using NSAIDs, nearly half (763/1691, 45%) attending for an FNA were deemed ineligible at different stages in the process because they failed our safety criteria. Our participants are likely to be younger and fitter than the typical patient being treated for knee pain in general practice; on average those we excluded on safety grounds were 3 years older than our participants. This should not affect the interpretation of our effectiveness results. Although the study had insufficient power to pick up differences in major adverse effects, it seems likely that our selection procedure produced a study population at lower risk of NSAID adverse effects than the general population of older people taking NSAIDs.

There is perhaps an issue about whether our safety criteria were too strict. Evidence from our Delphi study suggested that the level of screening that we applied before entering people into this study was in excess of that currently used in general practice. Therefore, the results of this study may not be directly applicable to those who have most to gain

from avoiding the toxicity of oral NSAIDs. The counterargument is that for those patients who fail our safety criteria, the risk of oral NSAIDs is always too great. In addition to having a different age and risk profile, the participants had to have persistent knee pain. The study excluded many patients with frequent but intermittent knee pain who are likely to be using NSAIDs in a primary care setting.

Potential for bias

No attempt was made to blind the study subjects or practices. This was deliberate so as to compare two forms of usual treatment, but this may have introduced bias in the questionnaires since these largely asked for subjective judgements by participants. The measurements taken by the research nurses used standardised equipment and should therefore be less prone to bias. Some of the adverse event measures, especially new diagnoses of heart failure and asthma, may have been subject to surveillance bias. Participants in the oral groups might have been more likely to have had additional blood tests organised by the general practice as part of routine care, making it more likely that abnormalities were identified. We are partly reassured that this did not occur because there does not appear to have been a difference in the numbers of such blood tests between the groups.

No attempt was made to change other aspects of participants' care. This means that they could have had variable numbers of co-interventions. We have good data on other pharmacological use, surgical interventions and hospital admissions but we do not have any data on the comparative exposure of the different groups to behavioural and exercise interventions.

Intention-to-treat or on-treatment analysis

It is usual, with equivalence studies, to do an on-treatment analysis rather than an intention-to-treat analysis. There are several inherent problems in doing an on-treatment analysis in this study.

The first is the difficulty interpreting the linear relationship between pain and treatment. Those with more underlying pain are likely to take more painkillers but still have more pain after taking the painkillers compared with those with little pain. Hence an on-treatment analysis is biased towards showing that those who take more treatment may have more pain. If both groups used their allocated painkillers similarly, this would not be a problem; however, this was unlikely to be true in this study. There was evidence from the trial that participants in the topical group were more likely to change treatment because it was felt to be inadequate, hence those remaining on topical treatment were likely to have less underlying pain than those remaining on, or subsequently changing to, oral NSAIDs.

Second, those changing to different oral NSAIDs were not considered to have changed treatment, so it was not always clear who changed from ibuprofen. Those changing topical treatment rarely changed to a 'stronger' topical treatment; they went straight to oral NSAIDs.

The final problem was that some patients bought their own treatments rather than going to the GP for a prescription, for which (1) we don't know how much they bought, if any, and (2) because it is clear from the data that some patients were confused between anti-inflammatory and other painkillers – we do not always know what they were taking. The prescription data and self-reported reasons for changing treatment are the most valid data we can offer in terms of on-treatment analyses. However, because of the problems inherent in these analyses, and that we were comparing effect of advice to use preferentially oral or topical NSAIDs rather testing the comparative efficacy of two preparations, it is appropriate for our main conclusions to be based on an intention-to-treat analysis.

Interpretation

Interpreting these results is not straightforward. What is clear is that the outcome from knee pain is equivalent whether oral or topical NSAIDs are advised. This could be because they are equally effective, because participants changed from less effective to more effective treatment or because neither oral nor topical NSAIDs have a meaningful beneficial effect on knee pain when used in the manner tested in this study. This finding of equivalence is consistent across the RCT and the PPS. Despite using a wide range of secondary outcome measures and carrying out multiple comparisons at different time-points, the only comparisons suggesting a difference in patient-centred outcomes were the change in chronic pain grade III/IV at 3 months and at the end of the study in the RCT and the fact that more participants reported changing treatment because of inadequate pain relief, again in the RCT. Both changes favour oral medication. The decision whether to recommend topical or oral ibuprofen needs to be grounded in other information. Factors to consider are as follows.

Adverse effects

Although not conclusive, there is a suggestion from the TOIB data that those who use oral in preference to topical NSAID medications have more respiratory complications and higher creatinine levels. The low incidence of major adverse effects and absence of any difference in overall number of gastrointestinal adverse effects may be due to the careful screening of potential study participants. Hence we expect that we have underestimated the 'real-life' incidence of minor adverse effects. The well-known risks of serious NSAID-related adverse effects need to be included in any consideration of the comparative risk of oral and topical ibuprofen.

Cost-effectiveness

The cost-effective analysis suggests that, if purchasers are willing to pay £8600–9100 per QALY over a 12-month horizon or £12,000–18,000 over a 24-month horizon, oral NSAIDs are cost-effective in the RCT. In addition, in the PPS, oral NSAIDs dominate topical NSAIDs, over 24 months, suggesting that, for those patients who wish to use them, oral NSAIDs are cheaper and have slightly more beneficial effect on overall health utility. There are two important caveats that make us question whether the cost per QALY in this analysis justifies the routine use of oral rather than topical NSAIDs. First, the absolute differences in costs and QALYs are small, meaning that the cost per QALY can be sensitive to small changes. Second, we may have underestimated the negative effect on quality of life and increased health costs of using oral NSAIDs in routine practice because of our rigorous safety exclusion criteria. It is for this latter reason that we have not simply used the cost per QALY data to inform our final conclusions, although we are aware that others may wish to interpret our data showing that advice to use oral NSAIDs is a cost-effective option when compared with topical NSAIDs. This cost-effectiveness argument for preferring oral to topical NSAIDs may be particularly apposite if patients are only prescribed them if they meet the safety criteria that we used for this study.

Patient preferences

When given a choice, three times as many participants selected topical rather than oral medication. Participants with more severe widespread pain chose oral rather than topical ibuprofen. Furthermore, those who selected oral NSAIDs appeared to be more tolerant of their adverse effects than those randomly allocated to the oral group, even though the PPS oral group took substantially more oral NSAIDs. Our PPS participants seemed to be making logical choices about which administration route to use.

Conclusions

The outcome data from participants in our study were very similar in terms of both efficacy and adverse effects, regardless of treatment group. The management of knee pain in primary care involves choosing a range of lifestyle, physical and pharmaceutical interventions that are appropriate for a particular patient. We conclude that where the use of an NSAID is considered appropriate, the best strategy for primary care practitioners treating older people with chronic knee pain would be to suggest treatment with topical agents in preference to oral NSAIDs, unless the patient has a strong desire to use oral treatment and is not at high risk of adverse effects from oral NSAID use.

We suggest this for the following reasons:

- We have demonstrated that the outcome in terms of pain and disability is equivalent between these two approaches.
- In the RCT, the topical NSAIDs were less expensive.
- There are ample external data on the potential for serious adverse effects from using oral NSAIDs.
- Even though some people advised to use topical NSAID will also take oral NSAIDs, on average, they are unlikely to consume more of them than those advised to take oral NSAIDs.
- Although we did not show an overall difference in adverse effects between oral and topical use, we did show an increase in respiratory adverse effects and raised serum creatinine in the RCT oral group, and an increase in costs for cardiovascular drugs.
- Our study population was at a lower risk of NSAID adverse effects than the overall population with chronic knee pain.
- We have shown that patients with chronic knee pain prefer topical treatment, especially if their pain is localised and intermittent.
- Our study shows that those whose preference was met were more adherent to their chosen medication.
- The results from the oral PPS group suggested that, in this group only, oral ibuprofen was both less expensive and more effective over 24 months.

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Contribution of authors

Deborah Ashby (Professor of Medical Statistics) had overall responsibility for statistical aspects of the study. She contributed to the analysis plan and the analyses, to writing the clinical results chapter and to the overall drafting the final report. Dawn Carnes (Research Fellow) conducted the qualitative preference study and contributed to the qualitative analyses and with SP she led drafting of the qualitative chapter. She contributed to interpreting the data and drafting of the final report. She project managed the production of the report. Emanuela Castelnuovo (Senior Health Economist) contributed to the economic analysis plan and carried out the main health economic analyses. She wrote the first draft of the health economics chapter and contributed to the overall drafting of the final report. Pamela Cross (Clinical Research Fellow) was the Trial Clinician and led developing the study paperwork, assisted with the management of the study and liaised with laboratories and general practices on medical matters. She wrote the MIQUEST searches and worked with the practice research nurses to identify the study participants. She conducted the Delphi survey and wrote the first draft of the Delphi chapter, and is a guarantor for this chapter. She also wrote the first draft of the discussion and contributed to the overall drafting of the final report. Geoff Harding [Senior Research Fellow (Primary Care)] was one of the original applicants. He designed and conducted the pilot qualitative study. He contributed to the analysis of qualitative data and drafting of the qualitative chapter. Enid Hennessy (Lecturer in Medical Statistics) took the lead for the production of the analysis plan and the statistical analyses. She led the production of the clinical results chapter. She is the guarantor for statistical aspects of the study. She contributed to the overall drafting of the final report. Louise Letley (Senior Nurse Manager) had overall responsibility for all nursing activity within the trial, including training and quality control through the GPRF regional training nurses. She contributed to the implementation of the trial design, selecting and recruiting participants and trial documentation, including standard operating procedures. She managed the recruitment of participating practices and contributed to overall drafting of the final report. Jeannett Martin (Senior International Liaison Officer) was one of the original applicants and member of the trial steering committee. She contributed to the development of the trial protocol and procedures, and developed fieldwork costings for the trial. As Senior Nurse Manager for the MRC General Practice Research Framework (until June 2004) she had overall responsibility for all nursing activity within the trial and developed the quality control procedures for the fieldwork which were included as an appendix of the report. She has approved the final version of the report. Shahrul

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Other members of the trial team

Yasir Anwer conducted the adverse effects interviews and contributed to the analysis and interpretation of the qualitative adverse events study. Valerie Brueton, GPRF Nurse, provided support for the GPRF nurses and assisted with the final data collection (from January 2006). Hansa Shah was the Study Administrator. She had responsibility for the data input and administration of the study. She organised the follow-up of all participants recruited into the study. Helen Tate was one of the original applicants. She contributed to the study design and development of the protocol.

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References

1. Gabriel SE. Update on the epidemiology of the rheumatic diseases. *Curr Opin Rheumatol* 1996;**8**:96–100.
2. Thomas E, Peat G, Harris L, Wilkie R, Croft PR. The prevalence of pain and pain interference in a general population of older adults: cross-sectional findings from the North Staffordshire Osteoarthritis Project (NorStOP). *Pain* 2004;**110**: 361–8.
3. Urwin M, Symmons D, Allison T, Brammah T, Busby H, Roxby M, *et al*. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. *Ann Rheum Dis* 1998;**57**:649–55.
4. O'Reilly SC, Muir KR, Doherty M. Screening for pain in knee osteoarthritis: which question? *Ann Rheum Dis* 1996;**55**:931–3.
5. Jinks C, Jordan K, Croft P. Measuring the population impact of knee pain and disability with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). *Pain* 2002;**100**: 55–64.
6. Jinks C, Jordan K, Ong BN, Croft P. A brief screening tool for knee pain in primary care (KNEST). 2 Results from a survey in the general population aged 50 or over. *Rheumatology* (Oxford). 2004;**43**:55–61.
7. Bedson J, Jordan K, Croft P. Chronic knee pain and osteoarthritis: an epidemiological study of labels, diagnosis and investigation in general practice. *Fam Pract* 2005;**22**:103–8.
8. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;**29**:1039–49.
9. Sharma L, Kapoor D, Issa S. Epidemiology of osteoarthritis: an update. *Curr Opin Rheumatol* 2006;**18**:147–56.
10. Peat G, Thomas E, Duncan R, Wood L, Hay E, Croft P. Clinical classification criteria for knee osteoarthritis: performance in the general population and primary care. *Ann Rheum Dis* 2006;**65**:1363–7.
11. Brooks P, Hochberg M. Outcome measures and classification criteria for the rheumatic diseases. A compilation of data from OMERACT (Outcome Measures for Arthritis Clinical Trials), ILAR (International League of Associations for Rheumatology), regional leagues and other groups. *Rheumatology (Oxford)* 2001;**40**:896–906.
12. Underwood MR. Community management of knee pain in older people: is knee pain the new back pain? *Rheumatology (Oxford)* 2004; **42**:1–2.
13. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000;**43**:1905–15.
14. Jawad AS. Analgesics and osteoarthritis: are treatment guidelines reflected in clinical practice? *Am J Ther* 2005;**12**:98–103.
15. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ* 2004;**329**:1317.
16. Chard J, Lohmander S, Smith C, Scott D. Osteoarthritis of the knee. *Clin Evid* 2005;1506–22.
17. Dieppe PA, Cushnaghan J, Jasani MK, McCrea F, Watt I. A two-year, placebo-controlled trial of non steroidal anti-inflammatory therapy in osteoarthritis of the knee joint. *Br J Rheumatol* 1993;**32**:595–600.
18. Scott DL, Berry H, Capell H, Coppock J, Daymond T, Doyle DV, *et al*. The long term effects of non-steroidal anti-inflammatory drugs in osteoarthritis of the knee: a randomised placebo-controlled trial. *Rheumatology (Oxford)* 2000;**39**: 1095–101.
19. Williams HJ, Ward JR, Egger MJ, Neuner R, Brooks RH, Clegg DO, *et al*. Comparison of naproxen and acetaminophen in a two year study of treatment of osteoarthritis of the knee. *Arthritis Rheum* 1993;**36**:1196–206.
20. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, *et al*. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006;**354**:795–808.
21. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, *et al*. MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with

osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006;**368**:1771–81.

22. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, *et al*. TARGET Study Group. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004;**364**:665–74.

23. Eccles M, Freemantle N, Mason J. North of England evidence based guideline development project: summary guideline for non-steroidal anti-inflammatory drugs versus basic analgesia in treating the pain of degenerative arthritis. The North of England Non-Steroidal Anti-Inflammatory Drug Guideline Development Group. *BMJ* 1998;**317**:526–30.

24. Boureau F, Schneid H, Zeghari N, Wall R, Bourgeois P. The IPSO study: ibuprofen, paracetamol study in osteoarthritis. A randomised comparative clinical study comparing the efficacy and safety of ibuprofen and paracetamol analgesic treatment of osteoarthritis of the knee or hip. *Ann Rheum Dis* 2004;**63**:1028–34.

25. Pincus T, Koch GG, Sokka T, Lefkowith J, Wolfe F, Jordan JM, *et al*. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 2001;**44**:1587–98.

26. Lee C, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum* 2004;**51**:746–54.

27. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006;(1):CD004257.

28. Wolfe F, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Arthritis Rheum* 2000;**43**:378–85.

29. OA Nation. *Arthritis care*. URL: http://oanation.arthritiscare.org.ukfileadmin/oanation/downloads/OA_Nation_report.pdf. Accessed 23 June 2006.

30. Pincus T, Swearingen C, Cummins P, Callahan LF. Preference for nonsteroidal antiinflammatory drugs versus acetaminophen and concomitant use of both types of drugs in patients with osteoarthritis. *J Rheumatol* 2000;**27**:1020–7.

31. Pincus T, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, *et al*. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004;**63**:931–9.

32. Henry D, Lim LL, Garcia Rodriguez LA, Perez GS, Carson JL, Griffin M, *et al*. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996;**312**:1563–6.

33. Peura DA, Goldkind L. Balancing the gastrointestinal benefits and risks of nonselective NSAIDs. *Arthritis Res Ther* 2005;**7** Suppl 4:S7–13.

34. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs* 2000;**60**:555–74.

35. Cooper C, Jordan KM. Topical NSAIDs in osteoarthritis. *BMJ* 2004;**329**:304–5.

36. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ* 2004;**329**:324.

37. Arthritis Research Campaign. Arthritis. The big picture. www.arc.org.uk/arthinfo/bigpic.asp. Accessed 23 February 2008.

38. Phillips AC, Polisson RP, Simon LS. NSAIDs and the elderly. Toxicity and economic implications. *Drugs Aging* 1997;**10**:119–30.

39. Langman MJ. Ulcer complications associated with anti-inflammatory drug use. What is the extent of the disease burden? *Pharmacoepidemiol Drug Saf* 2001;**10**:13–19.

40. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. *BMC Musculoskeletal Disord* 2004;**5**:28.

41. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. *Semin Arthritis Rheum* 1997;**26**:755–70.

42. Towheed TE. Published meta-analyses of pharmacological therapies for osteoarthritis. *Osteoarthritis Cartilage* 2002;**10**:836–7.

43. *British National Formulary*. 52nd ed. London: BMJ, Royal Pharmaceutical Society of Great Britain; 2006.

44. Blower AL, Brooks A, Fenn GC, Hill A, Pearce MY, Morant S, *et al*. Emergency admissions for upper gastrointestinal disease and their relation to NSAID use. *Aliment Pharmacol Ther* 1997;**11**:283–91.

45. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, *et al*. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;**123**:241–9.

46. Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case–control analysis. *BMJ* 2005;**331**:1310–16.

47. Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. *Pain* 2000;**85**: 169–82.

48. Field TS, Gurwitz JH, Glynn RJ, Salive ME, Gaziano JM, Taylor JO, *et al*. The renal effects of nonsteroidal anti-inflammatory drugs in older people: findings from the Established Populations for Epidemiologic Studies of the Elderly. *J Am Geriatr Soc* 1999;**47**:507–11.

49. Kleinknecht D, Landais P, Goldfarb B. Analgesic and non-steroidal anti-inflammatory drug associated acute renal failure: a prospective collaborative study. *Clin Nephrol* 1986;**25**:275–81.

50. Whelton A, Hamilton C. Non steroidal anti-inflammatory drugs: effects on kidney function. *J Clin Pharmacol* 1991;**31**:588–98.

51. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994; **121**:289–300.

52. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004; **328**:434.

53. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;**332**:1302–8.

54. Ray W, Stein M, Daugherty J, Hall K, Arbogast P, Griffin M. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002;**360**:1071–3.

55. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003;**361**: 573–4.

56. Rolf C, Engstrom B, Beauchard C, Jacobs LD, Le Liboux A. Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. *Rheumatology (Oxford)* 1999;**38**:564–7.

57. Dominkus M, Nicolakis M, Kotz R, Wilkinson FE, Kaiser RR, Chlud K. Comparison of tissue and plasma levels of ibuprofen after oral and topical administration. *Arzneimittelforschung* 1996;**46**: 1138–43.

58. Towheed TE. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol* 2006;**33**:567–73.

59. Vaile JH, Davis P. Topical NSAIDs for musculoskeletal conditions. A review of the literature. *Drugs* 1998;**56**:783–99.

60. Arcury TA, Gesler WM, Cook HL. Meaning in the use of unconventional arthritis therapies. *Am J Health Promot* 1999;**14**:7–15.

61. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004; **328**:991.

62. Michalsen A, Klotz S, Ludtke R, Moebus S, Spahn G, Dobos GJ. Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med* 2003;**139**:724–30.

63. Knuesel O, Weber M, Suter A. Arnica montana gel in osteoarthritis of the knee: an open, multicenter clinical trial. *Adv Ther* 2002;**19**:209–17.

64. Cohen M, Wolfe R, Mai T, Lewis D. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. *J Rheumatol* 2003;**30**:523–8.

65. Kimmey MB. NSAID, ulcers, and prostaglandins. *J Rheumatol* 1992;**19**(Suppl 36):68–73.

66. O'Callaghan CA, Andrews PA, Ogg CS. Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994;**308**:110–11.

67. Fraenkel L, Wittink DR, Concato J, Fried T. Informed choice and the widespread use of antiinflammatory drugs. *Arthritis Rheum* 2004;**51**:210–14.

68. Moore R, Phillips C. Cost of NSAID adverse effects to the UK National Health Service. *J Med Econ* 1999;**2**:45–55.

69. Bandolier. Topical analgesics: a review of reviews and a bit of perspective. URL: www.ebandolier.com. Bandolier Extra – Evidence-based health care. Accessed March 2005.

70. Watson MC, Brookes ST, Kirwan JR, Faulkner A. Non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2000;(2):CD000142.

71. Underwood MR. Is it safe for general practitioners to continue to use ibuprofen for older people with

musculoskeletal pain? *Rheumatology (Oxford)* 2003; **42** (Suppl 1):18.

72. Powell C. The Delphi technique: myths and realities. *J Adv Nurs* 2003;**41**:376–82.

73. Laine L. The gastrointestinal effects of non-selective NSAIDs and Cox-2-selective inhibitors. *Arthritis Rheum* 2002;**32** (Suppl 1):25–32.

74. Straus WL, Ofman JJ, MacLean C, Morton S, Berger ML, Roth EA, *et al*. Do NSAIDs cause dyspepsia? A meta-analysis evaluating alternative dyspepsia definitions. *Am J Gastroenterol* 2002;**97**(8):1951–8.

75. Wroblewski M, Ostberg H. Ulcer disease among geriatric patients with positive faecal occult blood test and/or iron deficiency anaemia. A prospective study. *Scand J Gastroenterol* 1990;**25**:489–95.

76. Brater DC. Anti-inflammatory agents and renal function. *Semin Arthritis Rheum* 2002;**32** (3 Suppl 1): 33–42.

77. Garcia Rodriguez LA, Hernandez-Diaz S. Nonsteroidal anti-inflammatory drugs as a trigger of clinical heart failure. *Epidemiology* 2003;**14**: 240–6.

78. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients. An underrecognized public health problem. *Arch Intern Med* 2000;**160**:777–84.

79. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. *Am J Med* 1999;**106**: 13s–24s.

80. Szczeklik A, Nizankowska E, Mastalerz L, Szabo Z. Analgesics and asthma. *Am J Ther* 2002;**9**: 233–43.

81. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999;**28**:717–22.

82. Picardo C. Mechanisms of aspirin sensitivity. *Cur Allergy Asthma Rep* 2006;**6**:198–202.

83. Cabral D, Katz JN, Weinblatt M, Ting G, Avom J, Soloman DH. Development and assessment of indicators of rheumatoid arthritis severity: results of a Dephi panel. *Arthritis Rheum* 2005;**53**:61–6.

84. Pendleton A, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JWJ, *et al*. 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). *Ann Rheum Dis* 2000;**59**:936–44.

85. Mitchell HL, Carr AJ, Scott DL. The management of knee pain in primary care: factors associated with consulting the GP and referrals to secondary care. *Rheumatology (Oxford)* 2006;**45**:771–6.

86. Hinman R, Crossley K, McConnell J, Bennell K. Efficacy of knee tape in the management of osteoarthritis of the knee: blinded randomised controlled trial. *BMJ* 2003;**327**:135.

87. Butler CC, Rollnick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 1998;**317**:637–42.

88. Gannik D, Jespersen M. Lay person concepts and strategies for handling symptoms of disease: a sample of adult male and female experience of back pain symptoms. *Scand J Primary Health Care* 1984;**2**:67–76.

89. Harding G, Parsons S, Rahman A, Underwood M. "It struck me that they didn't understand pain": the specialist pain clinic experience of patients with chronic musculoskeletal pain. *Arthritis Rheum* 2005;**53**:691–6.

90. Ross MM, Carswell A, Hing M, Hollingworth G, Dalziel WB. Seniors' decision making about pain management. *J Adv Nurs* 2001;**35**:442–51.

91. Torgerson D, Sibbald B. Understanding controlled trials: what is a patient preference trial? *BMJ* 1998;**7128**:360.

92. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. *BMJ* 1989;**299**:313–15.

93. King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*. Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials. *Health Technol Assess* 2005;**9**(35).

94. MRC. *Medical Research Council General Practice Research Framework*. http://www.gprf.mrc.ac.uk. Accessed 22 February 2008.

95. Jarman B. Identification of underprivileged areas. *Br Med J (Clin Res Ed)* 1983;**286**:1705–9.

96. Jarman B. Underprivileged areas: validation and distribution of scores. *Br Med J (Clin Res Ed)* 1984;**289**(6458):1587–92.

97. Bedson J, Mottram S, Thomas E, Peat G. Knee pain and osteoarthritis in the general population: what influences patients to consult? *Fam Pract* 2007;**24**:443–53.

98. Data Protection Act 1998. URL: http://www.opsi.gov.uk/ACTS/acts 1998/19980029.htm. Accessed 31 October 2007.

99. European Union. *Directive 2001/20/EC – 'Clinical Trials Directive*'. Brussels: European Union; 2001.

100. Neal RD, Heywood PL, Morley S. Real world data – retrieval and validation of consultation data from four general practices. *Fam Pract* 1996;**13**:455–61.

101. Jinks C, Lewis M, Ong BN, Croft P. A brief screening tool for knee pain in primary care. 1. Validity and reliability. *Rheumatology (Oxford)* 2001;**40**:528–36.

102. Johnson AG. NSAIDs and increased blood pressure. What is the clinical significance? *Drug Saf* 1997;**17**:277–89.

103. Lynfield YL, Schechter S. Choosing and using a vehicle. *J Am Acad Dermatol* 1984;**10**:56–9.

104. Azurdia RM, Pagliaro JA, Diffey BL, Rhodes LE. Sunscreen application by photosensitive patients is inadequate for protection. *Br J Dermatol* 1999;**140**: 255–8.

105. Finlay A, Edwards P, Harding K. Finger tip unit in dermatology. *Lancet* 1989;**ii**:155.

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

107. Bellamy N. *WOMAC Osteoarthritis Index. User Guide*, Version V. Brisbane, Australia; 2002.

108. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, *et al*. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *J Rheumatol* 1997;**24**:799–802.

109. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, *et al*. Gastrointestinal toxicity with celexicob vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000;**284**:1247–55.

110. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, *et al*. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;**343**:1520–8.

111. Brazier J, Jones N, Kind P. Testing the validity of the EuroQol and comparing it with the SF-36 health survey questionnaire. *Qual Life Res* 1993;**2**:169–80.

112. EuroQol – a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy* 1990;**16**:199–208.

113. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain* 1992;**50**:133–49.

114. Smith BH, Penny KI, Purves AM, Munro C, Wilson B, Grimshaw J, *et al*. The Chronic Pain Grade questionnaire: validation and reliability in postal research. *Pain* 1997;**71**:141–7.

115. Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *BMJ* 1993;**306**: 1440–4.

116. Ware JE, Kosinski M, Dewey JE. *How to score version 2 of the SF-36 health survey*. Lincoln, RI: Quality Metric; 2000.

117. Parsons S, Carnes D, Pincus T, Foster N, Breen A, Vogel S, *et al*. Measuring troublesomeness of chronic pain by location. *BMC Musculoskel Disord* 2006;**7**:34.

118. Cherkin DC, Deyo RA, Street JH, Barlow W. Predicting poor outcomes for back pain seen in primary care using patients' own criteria. *Spine* 1996;**21**:2900–7.

119. Underwood MR, Morton V, Farrin A, on behalf of the UK BEAM trial team. Baseline characteristics predict response to treatment for low back pain? Secondary analysis of the UK BEAM dataset [ISRCTN32683578]. *Rheumatology (Oxford)* 2007; **46**:1297–302.

120. Peloso PM, Bellamy N, Bensen W, Thomson GT, Harsanyi Z, Babul N, *et al*. Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol* 2000;**27**:764–71.

121. Cross PL, Ashby D, Harding G, Hennessy EM, Letley L, Parsons S, *et al*. TOIB Study. Are topical or oral ibuprofen equally effective for the treatment of chronic knee pain presenting in primary care: a randomised controlled trial with patient preference study. [ISRCTN79353052]. *BMC Musculoskelet Disord* 2005;**6**:55.

122. Drummond MF, O'Brien B, Stoddart GL, Torrence G. *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford: Oxford University Press; 1997.

123. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Econ* 1997;**6**:327–40.

124. HM Treasury. *The green book: appraisal and evaluation in central government*. London: Stationery Office; 2003.

125. Curtis L, Netten A. *Unit costs of health and social care*. Canterbury: University of Canterbury; 2005.

126. Department of Health. *NHS reference costs database for 2005*. London: Department of Health; 2005.

127. Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006;**10**(21).

128. NICE. *Clinical guideline N.3. Preoperative tests. The use of routine preoperative tests for elective surgery*.

London: National Institute for Health and Clinical Excellence; 2003.

129. Marsh F, Kremer C, Duffy S. Delivering an effective outpatient service in gynaecology. A randomised controlled trial analysing the cost of outpatient versus daycase hysteroscopy. *BJOG* 2004;**111**:243–8.

130. Dolan P, Gudex C, Kind P, Williams A. *A social tariff for EuroQOL of life: results from a general UK general population survey*. Discussion Paper 138. Oxford: Centre for Health Economics; 1995.

131. Willan AR, Lin DY, Manca A. Regression methods for cost-effectiveness analysis with censored data. *Stat Med* 2005;**24**:131–45.

132. Raftery J. Review of NICE's recommendations, 1999–2005. *BMJ* 2006;**332**:1266–8.

133. Charles C, Gafni A, Whelan T. Decision-making in the physician–patient encounter: revisiting the shared treatment decision-making model. *Soc Sci Med* 1999;**49**:651–61.

134. Thom D, Kravitz R, Bell R, Krupat E, Azari R. Patient trust in the physician: relationship to patient requests. *Fam Pract* 2002;**19**:476–83.

135. Awad MA, Shapiro SH LJ, Feine JS. Determinants of patients' treatment preferences in a clinical trial. *Community Dent Oral Epidemiol* 2000;**28**:119–25.

136. Borders T, Rohrer J, Xu T, Smith D. Older persons' evaluation of health care: the effects of medical scepticism and worry about health. *Health Serv Res* 2004;**39**:35–52.

137. Clark JP, Hudak PL, Hawker GA, Coyte PC, Mahomed NN, Kreder HJ, *et al*. The moving target: a qualitative study of elderly patients' decision-making regarding total joint replacement surgery. *J Bone Joint Surg Am* 2004;**86**-A(7): 1366–74.

138. Goodacre L, Goodacre J. Factors influencing the beliefs of patients with rheumatoid arthritis regarding disease modifying medication. *Rheumatology (Oxford)* 2004;**43**:583–6.

139. Fraenkel L, Bogardus S, Concato J, Felson D. Unwillingness of rheumatoid arthritis patients to risk adverse effects. *Rheumatology (Oxford)* 2002;**41**:253–61.

140. Sale J, Gignac M, Hawker G. How "bad" does the pain have to be? A qualitative study examining adherence to pain medication in older adults with osteoarthritis. *Arthritis Rheum* 2006;**55**:272–8.

141. Pound P, Britten N, Morgan M, Yardley L, Pope C, Daker-White G, *et al*. Resisting medicines: a synthesis of qualitative studies of medicine taking. *Soc Sci Med* 2005;**61**:133–55.

142. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In Bryman A, Burgess RG, editors. *Analysing qualitative data*. London: Routledge; 1994. pp. 173–94.

143. Stead M, Eadie D, Gordon D, Angus K. "Hello, hello – it's English I speak!": a qualitative exploration of patient understanding of the science of clinical trials. *J Med Ethics* 2005;**31**: 664–9.

144. Townsend A, Hunt K, Wyke S. Managing multiple morbidity in mid-life: a qualitative study of attitudes to drug use. *BMJ* 2003;**327**:837.

145. Victor C, Ross F, Axford J. Capturing lay perspective in a randomised control trial of a health promotion intervention for people with osteoarthritis of the knee. *J Eval Clin Pract* 2004;**10**:63–70.

146. Herve C, Mullet E, Sorum PC. Age and medication acceptance. *Exp Aging Res* 2004;**30**: 253–73.

147. Williams B, Shaw A, Durrant R, Crinson I, Pagliari C, de Lusignan S. Patient perspectives on multiple medication versus combined pills: a qualitative study. *Qual J Med* 2005;**98**:885–93.

148. Benson J, Britten N. What effects do patients feel from their antihypertensive tablets and how do they react to them? Qualitative analysis of interviews with patients. *Fam Pract* 2006;**23**:80–7.

149. Spinewine A, Swine C, Dhillon S, Franklin B, Tulkens P, Wilmotte L, *et al*. Appropriateness of use of medicines in elderly inpatients: qualitative study. *BMJ* 2005;**331**:935–8.

150. Stockl K, Cyprien L, Chang EY. Gastrointestinal bleeding rates among managed care patients newly started on cox-2 inhibitors or nonselective NSAIDs. *J Manage Care Pharm* 2005;**11**:550–8.

151. Praught ML, Shlipak MG. Are small changes in serum creatinine an important risk factor? *Curr Opin Nephrol Hypertens* 2005;**14**:265–70.

152. Shlipak MG, Stehman-Breen C, Vittinghoff E, Lin F, Varosy PD, Wenger NK, *et al*. Creatinine levels and cardiovascular events in women with heart disease: do small changes matter? *Am J Kidney Dis* 2004;**43**:37–44.

153. Segal L, Day SE, Chapman B, Osborne RH. Can we reduce disease burden from osteoarthritis? *Med J Aust* 2003;**180**(Suppl 5):s11–s17.

154. Nicolaides K, Brizot ML, Patel F, Snijders R. Comparison of chorionic villus sampling and amniocentesis for fetal karyotyping at 10–13 weeks' gestation. *Lancet* 1994;**344**:435–9.

155. Ashok PW, Hamoda H, Flett GM, Kidd A, Fitzmaurice A, Templeton A. Patient preference in a randomized study comparing medical and surgical abortion at 10–13 weeks gestation. *Contraception* 2005;**71**:143–8.

156. Olschewski M, Schumacher M, Davis KB. Analysis of randomized and nonrandomized patients in clinical trials using the comprehensive cohort follow-up study design. *Control Clin Trials* 1992;**13**:226–39.

157. Rabenda V, Burlet N, Raeman F, Belaiche J, Reginster J-Y. A naturalistic study of the determinants of health related quality of life improvement in osteoarthritic patients treated with non-specific non-steroidal anti-inflammatory drugs. *Ann Rheum Dis* 2005;**64**:688–93.

158. Bradley JD, Katz BP, Brandt KD. Severity of knee pain does not predict a better response to an antiinflammatory dose of ibuprofen than to analgesic therapy in patients with osteoarthritis. *J Rheumatol* 2001;**28**:932–4.

159. Hay E, Foster N, Peat G, Phelan M, Yates H, Bleckinsopp A, *et al*. Effectiveness of community physiotherapy and enhanced pharmacy review for knee pain in people aged over 55 presenting to primary care: pragmatic randomised trial. *BMJ* 2006;**333**:995.

160. van der Waal JM, Terwee CB, Dekker J. Health-related and overall quality of life of patients with chronic hip and knee complaints in general practice. *Qual Life Res* 2005;**14**:795–803.

161. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW, for the CONSORT group. Reporting of noninferiority and equivalence randomized trials. An extension of the CONSORT statement. *JAMA* 2006;**295**:1152–160.

Appendix 1

Delphi study questionnaire

Study Number

Barts and The London
Queen Mary's School of Medicine and Dentistry

Topical or Oral IBuprofen in chronic knee pain (TOIB)

GP expert panel consultation on minor side-effects

The TOIB study is comparing topical and oral ibuprofen in subjects aged 50 years or over who have chronic knee pain. The primary analysis will compare both the benefits of the two treatment approaches and the incidence of adverse events. We are collecting specific information, outlined below, on adverse effects.

We need the views of a panel of expert general practitioners to inform our interpretation of the data we collect on minor adverse events from non-steroidal anti-inflammatory drugs (NSAIDs); that is, adverse effects not requiring hospital treatment.

We would like your opinion on the level of the various possible side-effects at which you would recommend that a typical patient stops using an NSAID. Please indicate your opinion about the appropriateness of recommending that the patient should stop NSAID treatment in each proposed situation: 1 = highly inappropriate, 9 = highly appropriate. For some questions, you will be asked to indicate your choice of a point at which it would be appropriate to recommend stopping treatment. You will also be asked to give any opinions you may have on advice to stop NSAID treatment in the event of side-effects.

Section 1: Side-effects related to gastrointestinal irritation

A. Participants are asked about frequency of indigestion at baseline, and in follow-up questionnaires sent at 3, 6, 12 and 24 months. They are asked to grade their symptoms as number of days during the previous 3 months as follows:

- **No days**
- **A few days (occasionally)**
- **More than occasionally, but fewer than half the days**
- **Most days (half or more of the days)**
- **Every day**

Those answering 'most days' or 'every day' at baseline are not entered into the study.

Please indicate, for each of the following statements, your opinion on the appropriateness of advising a typical patient to stop NSAIDs, by circling the number or option that best indicates your opinion.

1. At which level of reported indigestion symptoms during the previous 3 months would you usually advise a typical patient to stop NSAID treatment?

A few days (occasionally)	More than occasionally, but fewer than half the days	Most days (half or more of the days)	Every day

2. 'It would usually be appropriate to advise a typical patient to stop NSAID treatment if s/he is reporting an increase of one category (e.g. from 'a few days' to 'more than occasionally') in indigestion symptoms since baseline'.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

3. 'It would usually be appropriate to advise a typical patient to stop NSAID treatment if s/he is reporting an increase of **more than** one category (e.g. from 'a few days' to 'most days') in indigestion symptoms since baseline'.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

4. If you have any other comments on stopping NSAID treatment in patients with indigestion, please write them here:

B. Haemoglobin will be measured at baseline, and at one and two years follow-up. Men with a haemoglobin <12.4, and women with a haemoglobin <11.8 at baseline, are not entered into the study.

Please indicate your opinion in the following questions, by entering a value for haemoglobin, or by circling the number that best indicates your opinion.

5a. Please enter in the box below the value for haemoglobin for a **male** patient > which you would have no concerns about the patient **continuing** on NSAID treatment.

5b. Please enter in the box below the value for haemoglobin for a **female** patient > which you would have no concerns about the patient **continuing** on NSAID treatment.

6a. Please enter in the box below the value for haemoglobin for a **male** patient < which you would have no hesitation in advising the patient to **stop** NSAID treatment.

6b. Please enter in the box below the value for haemoglobin for a **female** patient < which you would have no hesitation in advising the patient to **stop** NSAID treatment.

7. How great a fall in haemoglobin level from a baseline value would usually lead you to advise a typical patient to stop NSAID treatment? Please enter a figure in the box below.

C. Ferritin will be measured at baseline, and at one and two years follow-up. Subjects with a ferritin <12 μg/l at baseline will not be entered into the study. Normal range for ferritin varies considerably between different laboratories, but is approximately 12–400 μg/l.

Please indicate your level of agreement with the following statements, by circling the option that best indicates your opinion.

8. 'A typical patient should usually be advised to stop NSAIDs if the following drop in ferritin from baseline occurs' (without frank GI bleeding, or evidence of anaemia). Please circle the option that most closely matches your opinion.

   5 μg/l drop or less 10 μg/l drop 20 μg/l drop 30 μg/l drop or above

9. 'It would usually be appropriate to advise a typical patient to stop NSAIDs if the ferritin level falls below the normal range'. Please circle the number that best indicates your opinion.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

10. If you have any other comments on stopping NSAID treatment in patients with evidence of occult bleeding, please write them here:

Section 2: Cardiovascular/renal side-effects

A. BP is measured at baseline and at 1 and 2 years follow-up. Subjects with a BP persistently above 155/95 despite treatment will not be entered into the study. General practice notes will be searched at 1 and 2 years to find any new diagnosis of hypertension, or change in medication during the study.

Please indicate your level of agreement with the following statements, by circling the number or option that best indicates your opinion.

11. 'It would usually be appropriate to advise a typical patient to stop NSAIDs if there is a new diagnosis of hypertension after starting NSAID treatment'.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

12. 'It would usually be appropriate to advise a typical patient to stop NSAIDs if control of existing hypertension worsens after starting NSAID treatment, necessitating a change of antihypertensive therapy'.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

13. 'A typical patient should usually be advised to stop NSAIDs if the following rise in **systolic** blood pressure from baseline occurs'.

5 mmHg rise or less	10 mmHg rise	15 mmHg rise	20 mmHg rise	25 mmHg rise	30 mmHg rise or more

14. 'A typical patient should usually be advised to stop NSAIDs if the following rise in **diastolic** blood pressure from baseline occurs'.

5 mmHg rise or less	10 mmHg rise	15 mmHg rise	20 mmHg rise	25 mmHg rise	30 mmHg rise or more

15. If you have any other comments on stopping NSAID treatment in patients with hypertension, please write them here:

B. Creatinine is measured at baseline, and at 1 and 2 years. Subjects with a creatinine >140 mmol/l at baseline (considered to be abnormal for people aged over 65 years) will not be entered into the study.

Please indicate your opinion in the following questions, by entering a value of creatinine where requested, or by circling the option that best indicates your opinion.

16. Please enter in the box below the value for creatinine < which you would have no concerns about a typical patient **continuing** on NSAID treatment.

17. Please enter in the box below the value for creatinine > which you would have no hesitation in advising a typical patient to **stop** NSAID treatment.

18. 'A typical patient should be advised to stop NSAIDs if the following rise in creatinine occurs'. Please circle the option that best indicates your opinion.

10 mmol/l rise or less	15 mmol/l rise	20 mmol/l rise	25 mmol/l rise	30 mmol/l rise or more

C. General practice notes will be searched at 1 and 2 years for any diagnosis of heart failure.

Please indicate your level of agreement with the following statement, by circling the number that best indicates your opinion.

19. 'It would be appropriate to advise a typical patient to stop NSAIDs if there is a new diagnosis of heart failure'.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

20. If you have any other comments on stopping NSAID treatment in patients with renal insufficiency or side-effects related to sodium retention, please write them here:

Section 3: Bronchospasm

Peak flow rate (PFR) is measured at baseline and 1 and 2 years. GP notes will be searched for any new diagnosis of asthma or chronic obstructive pulmonary disease (COPD), or a new prescription for a bronchodilator or steroid inhaler.

Please indicate your level of agreement with the following statements, by circling the number that best indicates your opinion.

21. 'It would be appropriate to advise a typical patient to stop NSAIDs if there is a reduction in PFR of at least 15% since baseline'. Please circle the number that best indicates your opinion.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

22. 'It would be appropriate to advise a typical patient to stop NSAIDs if there is a new diagnosis of asthma since baseline'.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

23. 'It would be appropriate to advise a typical patient to stop NSAIDs if there is a new diagnosis of COPD since baseline'.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

24. 'It would be appropriate to advise a typical patient to stop NSAIDs if it becomes necessary to initiate additional treatment for asthma/COPD after starting NSAID treatment'. Please circle the number that best indicates your opinion.

Highly inappropriate	1	2	3	4	5	6	7	8	9	Highly appropriate

25. If you have any other comments on stopping NSAID treatment in patients with bronchospasm, please write them here

Section 4: Other comments

26. If you have any other comments on minor adverse effects of NSAIDs, please write them below.

Thank you for your help. The answers from this questionnaire will be summarised and sent to you in the next round.

Please return this questionnaire in the envelope provided or return to:
Dr Pamela Cross
Dept of General Practice & Primary Care
2nd Floor Medical Science Block
FREEPOST (LON 2076)
London E1 4BR

Appendix 2

GPRF quality control documentation

Procedure for quality control within MRC General Practice Research Framework

Procedure for Quality Control within MRC General Practice Research Framework

SOP no: GPRF/A23/1

Written by: **Jeannett Martin** **Signed:** _____

Date: **7 January 2002**

Revised by: **Louise Letley** **Signed:** _____

Date: **5 December 2006**

Copied for reference to:

Regional Nurses, Senior Research Nurses, Study Managers, Administration Manager

Circulated for information to:

SCOPE:

MRC Good Clinical Practice requires that systems and procedures that assure the appropriate quality of every aspect of a trial are in place.

This procedure specifies the process for quality control visits undertaken by Regional Training Nurses for multi-centre studies within the MRC General Practice Research Framework.

DEFINITIONS:

Senior nurse manager – Nurse based at MRC GPRF co-ordinating centre with overall responsibility for nursing aspects of GPRF studies; accountable to the Head of the GPRF.

Regional nurse (RN) – Nurse with responsibility for supporting active GPRF practices within a geographical area; accountable to senior nurse manager.

Senior research nurse – Nurse based at GPRF co-ordinating centre with the nursing lead for specific studies; accountable to senior nurse manager.

Quality assurance – Actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with MRC guidelines for Good Clinical Practice (GCP) and the applicable regulatory requirements.

Quality control (QC) – operational techniques and activities undertaken within the quality assurance system to verify that the requirements for the quality of the trial related activities have been fulfilled.

PROCEDURE:

Before the quality control visit

1. The senior nurse manager will undertake a risk assessment based on the level of patient contact, potential for any harm and complexity of the trial protocol. For example questionnaire surveys with no patient interviews will require no routine practice QC visits, but trials will require QC at patient consent stage and at further patient interviews if there is potential for the quality of data to be compromised.

2. The senior nurse manager will advise the principal investigator on the number of quality control visits required before the grant application is made.
3. The senior nurse manager and senior research nurse for the study will draft the quality control (QC) form which will be circulated to the study manager and Regional Nurses for comments.
4. The final version of the QC form will be provided to senior research nurses and RNs electronically and also in paper form. This will include, as appropriate, items relating to the following areas:
    - Administration
        - Consent forms for all patients included in the research
        - Laminated GPRF notice in waiting room
        - Secure storage of patient documentation
        - Secure storage of equipment
        - Flagging of NHS notes
    - Data collection
        - Laptop computers
            - Data backup and transfer
            - Competence at using computer programs and management of paper forms
        - Paper forms – check a sample
            - Patients exist and are alive
            - Completed legibly
            - Corrections crossed through, dated and signed
    - Patient management
        - Patients identified according to protocol
        - All eligible patients contacted
        - Clinical measurements undertaken according to protocol
        - Adherence to scheduled visits
        - Recording contact regarding patient management
        - Code breaks undertaken according to protocol
        - Checking that patients have carrying card
    - Medication
        - Kept in locked cupboard and checked before supplied to patient
        - Compliance checked, unused drugs disposed of correctly and documentation submitted
5. Further supplies of the QC form can be requested by RNs from the senior research nurse for the individual study.
6. The senior research nurses in liaison with the study manager will develop a spreadsheet of estimated dates for each practice to receive a QC visit.
7. The senior research nurse will review practice QC visits undertaken during the study and provide quarterly reports on those outstanding to RNs.
8. RNs will contact trial nurses in their practices and arrange to visit for Quality Control. The RN will ask the trial nurse to contact patients before the QC visit and ask for permission for the RN to observe the interview.
9. The RN will write and confirm the date and time of visit.

During the quality control visit

10. The RN will check with each patient when they arrive that they are willing for her to be present during the interview.
11. The RN will observe at least one patient interview, where appropriate, and complete the quality control form.
12. If there are any aspects relating to patient safety e.g. wrong medication about to be given then the RN will intervene during the interview, but generally the RN will discuss the interview with the nurse after the patient has left.
13. Any aspects that need to be addressed will be brought to the nurse's attention and the RN will outline proposed action in comments box and sign the form.
14. The trial nurse will be given the opportunity to read form and RNs comments. She will then be given an opportunity to write her own comments and sign the form.
15. Further visits to be arranged depending on outcome of QC (see flow chart attached)
    - If satisfactory, the RN will book further visits with the nurse according to study schedule

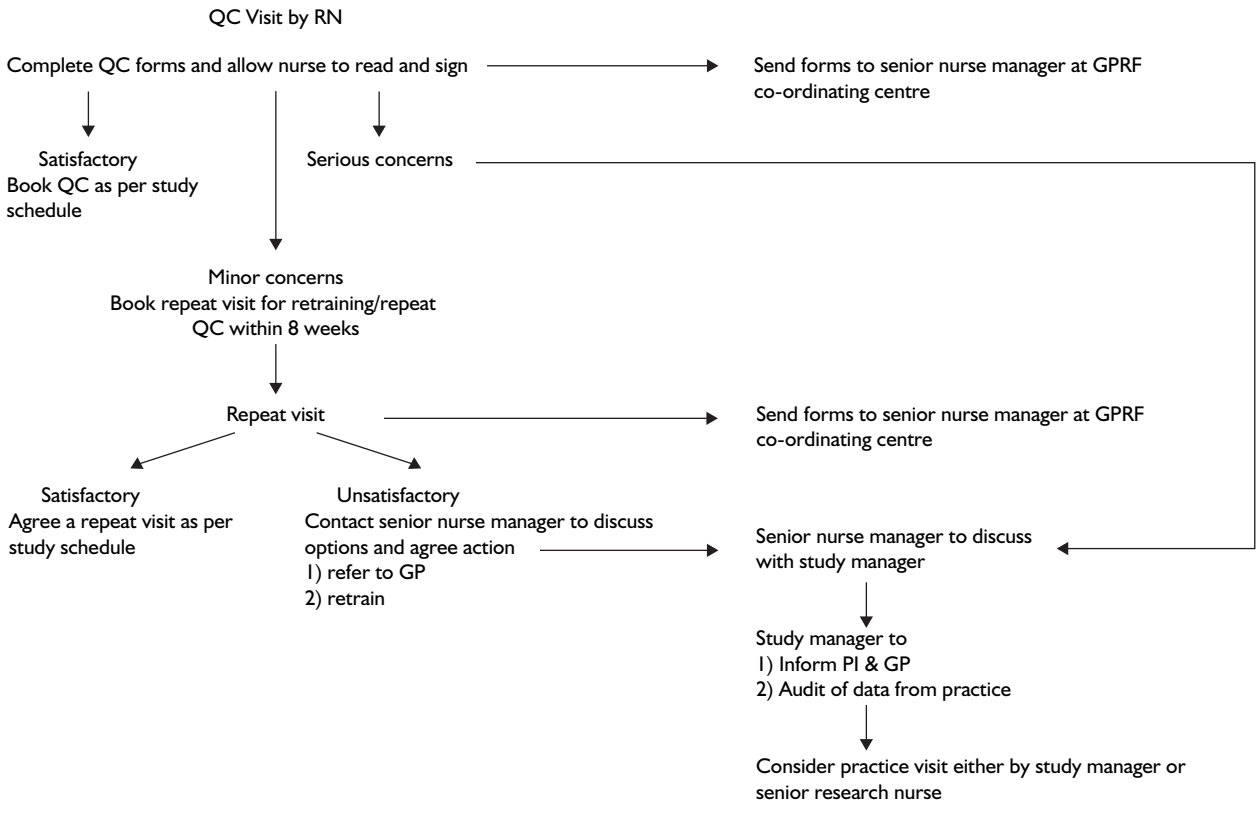
- If there are minor concerns, the RN will review procedures/provide further training and book a repeat visit as soon as possible. If this remains unsatisfactory the RN will contact the senior nurse manager to discuss options
- If there are serious concerns, e.g. patient safety or breach of protocol that would compromise trial data, the RN will contact co-ordinating centre for advice

16. RNs will be observed annually by the senior nurse manager while undertaking a QC visit.

After the quality control visit

17. Satisfactory
    - The RN will repeat QC visit according to study schedule and send in QC forms to senior nurse manager
18. Minor concerns identified
    - The RN will send in QC forms and repeat QC visit within 8 weeks. If concerns are resolved, further QCs will be arranged according to study schedule. If not resolved, the RN will contact the senior nurse manager to discuss
    - The senior nurse manager will inform study manager
    - The study manager will consider need to:
      - audit data submitted by practice and, if any anomalies, arrange for a full practice audit visit either by study manager or senior research nurse; and/or
      - contact GP to discuss situation
19. Serious concerns identified:
    - The RN will fax the QC forms and phone the senior nurse manager to discuss as soon as possible
    - The senior nurse manager will inform the study manager
    - Study manager will as soon as possible:
      - arrange for an audit of data submitted by practice and if any anomalies arrange for a full practice audit visit either by study manager or senior research nurse; and
      - contact GP to discuss situation

Procedure for quality control visit by research nurse



MRC General Practice Research Framework

Topical or Oral Ibuprofen
(TOIB)

Quality Control Form

Clinic No _____ Trial Nurse _____

Date of Visit _____ Regional Trainer _____

Did you observe a patient interview? YES ☐ NO ☐

If 'Yes', which interview? **first assessment/study entry assessment**
Delete as appropriate

Follow-up visit required YES ☐ NO ☐

Please return to Jeannett Martin, Senior Nurse Manager, Stephenson House, 158–160 North Gower Street, London NW1 2ND

1.	GENERAL	Yes	No
1.1	Do you consider that the nurse understands: • aims of the study? • importance of recruiting the maximum number of patients? • inclusion and exclusion criteria?		
1.2	Is the nurse adhering to the estimated times for the nurse assessments?		
1.3	Is the MRC research notice displayed in the waiting room? (if not, please ask nurse to inform practice manager)		
1.4	Does the practice leaflet contain information about MRC research? (if not, please ask nurse to inform practice manager)		

2.	**FORMS** ***(Please look at the study register & any completed questionnaires)***	**Yes**	**No**
2.1	Are the study forms stored in a locked cupboard or cabinet?		
2.2	Is the nurse able to identify the different study forms and when they should be used?		
2.3	Is the patient's study number entered on every questionnaire?		
2.4	Are the questionnaires • fully and correctly completed? • neat and legible?		
2.5	Does the nurse strike through an incorrect entry with a single line, and initial and date the correction?		
2.6	Are completed forms posted to the coordinating centre weekly?		

3.	**First Nurse Assessment** **Please complete if observed**	**Yes**	**No**
3.1	Does the nurse give the patient: • a clear correct explanation of the study? • an opportunity to ask questions? • a study information leaflet?		
3.2	Does the nurse ask the patient to complete & sign the first nurse assessment & notesearch consent forms? • does the nurse check that the consent forms have been completed correctly? • have all the consent forms been signed by the participant? *Please check and initial* • have the top copies been sent to the coordinating centre? • has the patient been given a copy of each for their records? • is a copy kept in the patient's trial folder at the practice?		
3.3	When completing the study entry assessment form is the nurse aware that answers in the shaded boxes: • make the patient ineligible? • result in termination of the interview?		
3.4	Is the nurse excluding patients with BP > 210/120? Is the nurse referring patients with raised BP according to usual practice policy?		
3.5	Does the nurse take bloods for FBC, ferritin, U&E and LFTs?		
3.6	Does the nurse organise a GP medical assessment for the patient?		
3.7	Does the nurse ask the patient to avoid using NSAIDS, if possible, in the week before their next appointment?		

4.	**Study entry assessment** *(Please complete if observed)*	**Yes**	**No**
4.1	When completing the study entry assessment form is the nurse aware that answers in the shaded boxes • make the patient ineligible? • result in termination of the interview?		
4.2	Is the nurse excluding patients with BP > 210/120? Is the nurse referring patients with raised BP according to usual practice policy?		
4.3	Is the nurse measuring the patient's peak flow correctly?		
4.4	Is the nurse measuring: • height in cm (without shoes)? • weight in kg (in indoor clothing)?		
4.5	Is the nurse excluding patients with: • creatinine >140 mmol/l? • Hb <12.4 g/l (men), <11.8 (women)?		
4.6	Are patients with abnormal blood results being referred according to usual practice policy?		
4.7	Does the nurse ask patients who are unwilling to be randomised, to join PPS?		
4.8	Does the nurse ask patient to complete the appropriate consent form (RCT or PPS)? • does the nurse check that the form has been completed correctly? • has the consent form been signed? • has the top copy been sent to the coordinating centre? • has the patient been given a copy? • is a copy kept in the patient's trial folder at the practice?		
4.9	Does the nurse check that the patient has completed all the questions in the study questionnaire?		

5.	**Study entry**	**Yes**	**No**
5.1	Does the nurse carry out the procedure for study entry/randomisation correctly? • does the nurse complete the registration/randomisation form before contacting the randomisation service? • do you consider that the nurse understands the procedure for study entry out of office hours?		
5.2	Does the nurse provide patients with: • allocation (if joining RCT)? • supply of allocated/chosen treatment? • appropriate information sheet? • carrying card • change of address form & prepaid envelope		
5.3	Does nurse flag computer prescribing record re study participation?		
5.4	Does nurse fix a TOIB sticker to paper records (if used)		
5.5	Does nurse remind patients re frequency of follow up questionnaires?		

6.	**Follow-up & notesearch *(for discussion)***	**Yes**	**No**
6.1	Do you consider that the nurse understands the follow-up assessment timetable & procedures?		
6.2	Have you discussed the procedure for notesearch with the nurse at this visit?		
6.3	Do you consider that the nurse understands the notesearch procedures?		

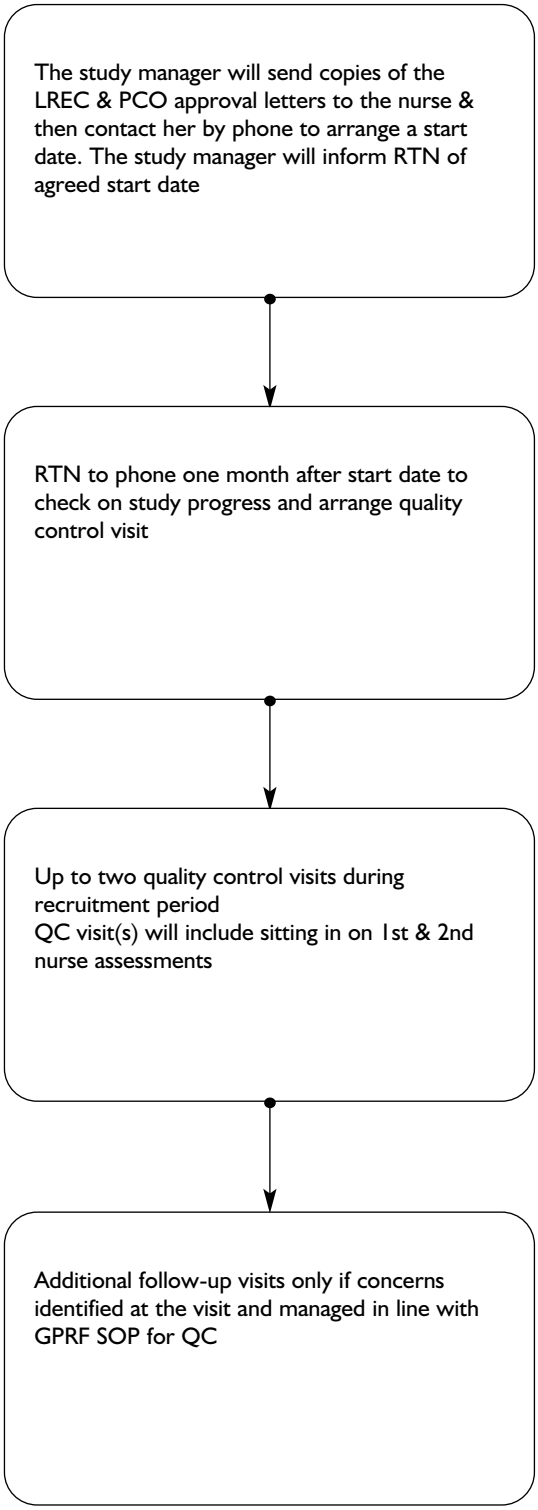
Regional Trainer comments (to be completed before the nurse signs form)

Signature of Regional Trainer _____

Trial nurse comments

Trial nurse signature _____

TOIB Quality Control Schedule



Appendix 3

Health economic evaluation (unit costs used in the cost-effectiveness analysis)

Unit costs are presented in *Tables 97–104*.

TABLE 97 *Unit costs for outpatient consultations in secondary care*

Outpatient consultation	Cost (£)
General surgery	113
Urology	106
Trauma and orthopaedics	103
ENT	88
Ophthalmology	72
Oral surgery	91
Orthodontics	100
Accident and emergency	94
Pain management	123
General medicine	135
Gastroenterology	119
Endocrinology	138
Clinical haematology	113
Audiological medicine	109
Clinical immunology and allergy	242
Rehabilitation	186
Cardiology	118
Dermatology	83
Respiratory medicine	152
Neurology	196
Clinical neurophysiology	115
Rheumatology	146
Geriatric medicine	180
Gynaecology	107
Clinical oncology	109
Podiatry	29
ECG	26
ECHO	61
Mental health psychiatrist	222
Dietary advice	52
Counselling	24
Diagnostic endoscopy for gastrointestinal bleed	285
Radiology services (direct access)	39

TABLE 98 *Admissions included and unit costs, day cases, elective and non-elective admissions (mean costs)*

Cause of admission	Cost (£)			
	Day case	Elective	Non-elective	Unspecified
Percutaneous image controlled pain procedures	544	2483	2312	2476
Haemorrhagic verebrovascular disorders	548	5264	4100	4135
Transient ischaemic attack >69 or w cc	528	3408	1550	1564
Non-transient stroke or cerebrovascular accident >69 or w cc	877	5658	4610	4631
Headache or migraine >69 or w cc	429	2414	1221	1252
Intermediate mouth or throat procedures	630	1263	2191	1363
Other respiratory diagnoses >69 or w cc	535	2563	1787	1827
Other respiratory diagnoses <70 w/o cc	488	2526	1010	1093
Pulmonary oedema	464	3406	2089	2130
Coronary bypass	1301	8862	9542	9015
Cardiac catheterisation and angiography with complications	682	3362	4234	4045
Percutaneous coronary intervention	2424	3215	3947	3560
Heart failure or shock >69 or w cc	445	4391	2656	2691
Deep vein thrombosis <70 w/o cc	343	1032	1041	1041
Arrhythmia or conduction disorders >69 or w cc	524	1890	1835	1837
Arrhythmia or conduction disorders <70 w/o cc	555	1279	919	936
Syncope or collapse <70 w/o cc	387	1541	768	781
Chest pain >69 or w cc	546	2193	1008	1017
Chest pain <70 w/o cc	603	1533	664	669
Diagnostic procedures oesophagus and stomach	409	1124	2886	1976
Disorders of the oesophagus >69 or w cc	374	2734	2812	2801
Large intestine – endoscopic or intermediate procedures	494	980	1613	1214
General abdominal – diagnostic procedures	584	2197	2962	2757
General abdominal disorders <70 w/o cc	368	1696	962	976
Primary knee replacement	5374	6121	8894	6135
Joint replacements or revisions site unspecified	2700	4471	6975	4583
Arthroscopies	959	1497	2551	1603
Foot procedures – category 1	673	1445	2730	1506
Hand procedures – category 1	720	1218	2434	1311
Soft tissue or other bone procedures – category 1 >69 or w cc	718	2370	5764	3314
Soft tissue or other bone procedures – category 1 <70 w/o cc	872	1946	3038	2094
Minor procedures to the musculoskeletal system	586	967	1036	985
Soft tissue disorders <70 w/o cc	414	1393	686	732
Closed pelvis or lower limb fractures >69 or w cc	833	5100	5164	5163
Closed pelvis or lower limb fractures <70 w/o cc	1038	2383	2851	2828
Closed upper limb fractures or dislocations >69 or w cc	980	2950	3156	3142
Closed upper limb fractures or dislocations <70 w/o cc	1006	2018	1893	1910
Sprains, strains or minor open wounds <70 w/o cc	690	1328	852	859
Other wounds or injuries	53	1700	1366	1374
Resurfacing of hip		5379	6126	5382
Revisional procedures to knees	1367	7603	9429	7840
Primary hip replacement cemented	4091	5741	7717	5805
Complex elderly with a skin breast or burn primary diagnosis	434	7327	4618	4736
Kidney or urinary tract infections >69 or w cc	434	3385	2809	2816
Kidney or urinary tract infections <70 w/o cc	323	1669	1076	1086
Bladder or urinary mechanical problems <70 w/o cc	357	1089	937	951
Prostate or bladder neck intermediate endoscopic procedure (male and female)	832	1499	3061	1604
Lower genital tract intermediate procedures	605	1180	1587	1286
Upper genital tract major procedures	1048	2924	3645	2975
Non-surgical treatment of fibroids menstrual disorders or endometriosis	372	993	769	779
Asthma or wheezing	449	1383	799	803
Lower respiratory tract disorders without acute bronchiolitis	550	3469	1470	1515
Minor infections (including immune disorders)	460	1551	942	955
Ingestion poisoning or allergies	614	891	694	695
Decompression and effusion for degenerative spinal disorders	1972	5787	8422	6235
Complications of procedures	439	3466	1966	2095

w cc, with complications, w/o cc, without complications.

TABLE 99 *Admissions excluded*

Cause of admission	Cost (£)			
	Day case	Elective	Non-elective	Unspecified
Lower limb arterial surgery	1284	5478	7285	6261
Varicose vein procedures	871	1435	4468	1597
Inguinal umbilical or femoral hernia repairs >69 or w cc	864	1621	2993	1837
Inguinal umbilical or femoral hernia repairs <70 w/o cc	897	1405	1791	1454
Malignant prostate disorders	333	1992	3199	2874
Phakoemulsification cataract extraction and insertion of lens	729	1431	2427	1466
Oculoplastic low complexity	604	1290	1481	1402
Anus – intermediate procedures >69 or w cc	674	1402	1827	1561
Anus – minor procedures >69 or w cc	527	1212	2170	1422
Cholecystectomy <70 w/o cc	1148	2007	3281	2165
Minor skin procedures – category 1 w/o cc	543	1392	1391	1391
Minor dermatological conditions or benign tumours	468	2081	1517	1616
Intermediate nose procedures	872	1302	1687	1392
Intermediate maxillo-facial/ENT procedures	799	1784	2115	2020
Minor ear procedures	662	1144	1496	1261
Minor nose procedures	626	1153	1205	1181
Extracorporeal lithotripsy	514	1233	1911	1533

TABLE 100 *Healthcare costs by subgroups: mean drug costs, by study, drug group and gender*

	Cost, RCT (£)				Cost, PPS (£)			
	Oral		Topical		Oral		Topical	
	Males	Females	Males	Females	Males	Females	Males	Females
12-month follow-up								
Oral ibuprofen	9.67	7.53	1.16	0.41	12.55	9.68	0.96	0.65
Other oral NSAIDs	5.12	12.01	12.22	11.73	16.05	11.81	3.46	4.68
Topical ibuprofen	0.10	0.49	15.84	15.40	0.00	0.00	22.80	16.00
Other topical NSAIDs	0.70	0.45	0.09	0.00	0.00	0.00	0.00	0.00
Other topical ointments	0.16	0.12	0.32	0.02	2.08	0.06	0.04	0.08
Paracetamol	6.46	6.64	5.41	3.59	11.49	7.94	5.59	6.41
Aspirin	1.62	0.62	1.15	0.60	2.22	0.14	1.41	0.95
Mild opioids	0.74	0.84	0.03	0.00	0.15	0.11	0.48	0.03
Strong opioids	0.39	5.15	0.06	2.54	3.92	4.02	0.14	6.32
Cardiovascular drugs	69.57	44.42	35.47	28.30	76.91	26.97	56.28	41.89
Indigestion and gastrointestinal	23.49	11.14	8.76	15.77	16.99	2.85	9.64	9.06
Other drugs	133.08	190.03	123.48	94.61	171.32	74.44	161.51	126.59
24-month follow-up								
Oral ibuprofen	17.09	13.26	2.33	0.21	17.78	16.48	2.66	1.25
Other oral NSAIDs	2.30	10.81	31.17	11.80	29.34	22.13	7.78	12.00
Topical ibuprofen	0.17	0.26	24.07	21.59	0.00	0.00	34.67	26.02
Other topical NSAIDs	0.00	1.27	0.00	0.00	0.13	0.00	0.10	0.10
Other topical ointments	0.28	0.19	0.39	0.03	3.20	0.03	0.21	0.44
Paracetamol	10.42	15.86	11.59	7.22	16.12	9.26	7.94	9.56
Aspirin	1.41	0.56	3.05	1.37	3.08	0.48	2.72	1.70
Mild opioids	0.00	0.10	0.00	0.00	0.13	0.09	1.39	0.83
Strong opioids	0.39	15.30	0.35	1.17	5.41	5.07	0.04	11.72
Cardiovascular drugs	113.42	58.51	40.58	45.07	110.74	38.04	99.80	73.20
Indigestion and gastrointestinal	50.08	23.28	12.11	17.49	9.99	6.20	17.45	22.77
Other drugs	282.09	165.66	112.23	199.13	218.81	155.54	341.03	228.15

TABLE 101 *Healthcare costs by subgroups: mean cost of care, by study, type of service and gender*

	Cost, RCT (£)				Cost, PPS (£)			
	Oral		Topical		Oral		Topical	
	Males	Females	Males	Females	Males	Females	Males	Females
12-month follow-up								
GP and nurse consultations	143.50	137.69	127.10	139.46	122.24	135.85	145.41	132.87
Outpatient consultations	89.01	70.90	48.45	67.62	54.10	64.88	66.12	76.01
Diagnostic tests	16.30	20.78	11.70	13.89	19.83	20.55	24.44	22.69
Equipment and aids	10.76	6.78	0.95	4.58	0.42	2.13	0.85	4.21
Hospital admissions	498.12	460.58	564.30	149.20	426.50	558.79	632.10	158.83
Prescription costs (relevant only)	118.02	89.40	80.49	78.35	142.36	63.57	100.81	86.07
Total	**875.71**	**786.13**	**833.00**	**453.08**	**765.45**	**845.78**	**969.73**	**480.69**
24-month follow-up								
GP and nurse consultations	216.50	229.05	255.87	262.41	230.29	239.54	245.86	232.93
Outpatient consultations	139.48	107.75	138.35	127.83	96.84	105.59	126.80	120.18
Diagnostic tests	25.08	27.02	19.63	23.03	25.75	24.65	44.72	25.94
Equipment and aids	10.40	4.23	1.79	1.31	0.90	2.35	2.79	6.90
Hospital admissions	625.56	692.86	618.99	383.27	433.78	746.79	981.32	700.29
Prescription costs (relevant only)	195.56	139.40	125.64	105.95	195.92	97.78	174.76	159.59
Total	**1212.58**	**1200.31**	**1160.27**	**903.80**	**983.48**	**1216.70**	**1576.25**	**1245.83**

TABLE 102 *Healthcare costs by subgroups: mean drug costs, by study, drug group and age*

	Cost, RCT (£)				Cost, PPS (£)			
	Oral		Topical		Oral		Topical	
	>Median age	<Median age	>Median age	<Median age	>Median age	<Median age	>Median age	<Median age
12-month follow-up								
Oral ibuprofen	9.38	7.47	0.86	0.70	12.80	9.05	0.86	0.68
Other oral NSAIDs	8.85	9.16	20.70	2.71	20.51	7.27	1.66	7.64
Topical ibuprofen	0.53	0.09	22.04	8.81	0.00	0.00	22.08	14.47
Other topical NSAIDs	1.06	0.02	0.00	0.09	0.00	0.00	0.00	0.00
Other topical ointments	0.13	0.14	0.09	0.24	1.75	0.07	0.04	0.09
Paracetamol	8.49	4.46	5.17	3.77	11.78	7.18	6.90	4.89
Aspirin	1.86	0.19	1.33	0.38	1.08	0.85	1.54	0.59
Mild opioids	0.94	0.64	0.00	0.03	0.00	0.23	0.38	0.01
Strong opioids	0.46	5.90	0.83	1.82	1.51	6.16	3.51	3.93
Cardiovascular drugs	76.83	32.16	42.59	20.43	48.90	44.51	61.51	29.24
Indigestion and gastrointestinal	23.08	9.43	17.04	7.30	3.22	12.96	8.10	10.98
Other drugs	213.53	112.49	146.69	68.73	80.82	140.33	179.66	88.29
24-month follow-up								
Oral ibuprofen	16.23	13.44	1.23	1.13	20.52	13.83	2.04	1.45
Other oral NSAIDs	4.29	10.33	33.69	5.35	34.52	16.57	6.19	16.31
Topical ibuprofen	0.27	0.17	30.88	13.11	0.00	0.00	36.35	19.43
Other topical NSAIDs	1.30	0.00	0.00	0.00	0.00	0.10	0.14	0.05
Other topical ointments	0.29	0.17	0.03	0.39	2.80	0.03	0.23	0.53
Paracetamol	19.82	5.85	9.50	8.91	14.47	9.99	11.26	5.61
Aspirin	1.60	0.15	3.46	0.58	2.09	1.08	2.78	1.12
Mild opioids	0.10	0.00	0.00	0.00	0.00	0.21	1.76	0.03
Strong opioids	2.00	16.69	1.34	0.15	2.91	7.32	6.24	8.54
Cardiovascular drugs	92.02	71.86	55.79	27.93	88.07	50.45	110.13	45.56
Indigestion and gastrointestinal	47.89	19.93	20.23	8.89	7.01	8.50	18.19	24.30
Other drugs	288.62	131.98	199.14	112.22	170.31	192.65	345.61	166.83

TABLE 103 *Healthcare costs by subgroups: mean cost of care, by study, type of service and age*

	Cost, RCT (£)				Cost, PPS (£)			
	Oral		Topical		Oral		Topical	
	>Median age	<Median age	>Median age	<Median age	>Median age	<Median age	>Median age	<Median age
12-month follow-up								
GP and nurse consultations	154.72	124.48	164.48	100.39	133.76	127.65	159.08	109.14
Outpatient consultations	72.27	85.95	72.03	43.50	51.69	68.55	74.90	67.46
Diagnostic tests	22.37	14.96	15.29	10.18	21.82	18.90	26.16	19.65
Equipment and aids	7.02	10.15	4.19	1.31	3.09	0.02	4.32	0.64
Hospital admissions	775.32	152.74	253.90	459.54	748.85	293.72	495.67	172.73
Prescription costs (relevant only)	131.60	69.66	110.65	46.28	101.54	88.27	106.59	72.53
Total	**1163.31**	**457.94**	**620.55**	**661.20**	**1060.76**	**597.10**	**866.71**	**442.16**
24-month follow-up								
GP and nurse consultations	225.26	221.38	288.22	225.43	230.78	240.16	262.62	202.76
Outpatient consultations	110.91	134.82	155.79	105.37	88.96	113.81	130.63	111.50
Diagnostic tests	33.97	16.84	24.25	18.18	23.39	26.68	38.99	25.00
Equipment and aids	4.09	10.40	2.28	0.65	3.62	0.03	7.12	2.72
Hospital admissions	784.61	517.84	742.59	195.17	915.32	342.31	1078.18	425.75
Prescription costs (relevant only)	185.81	138.59	156.15	66.44	172.39	108.08	195.31	122.93
Total	**1344.65**	**1039.87**	**1369.28**	**611.24**	**1434.45**	**831.06**	**1712.84**	**890.65**

TABLE 104 *Model specification for the conversion of EQ-5D data into quality of life weights*

Dimension	Coefficient
Full health	1.000
Constant term (for any dysfunctional state)	–0.081
Mobility	
Level 2	0.069
Level 3	0.314
Self-care	
Level 2	0.104
Level 3	0.241
Usual activity	
Level 2	0.036
Level 3	0.094
Pain/discomfort	
Level 2	0.123
Level 3	0.386
Anxiety/depression	
Level 2	0.071
Level 3	0.236
At least one level 3 dimension	0.269
Adjusted R^2	0.460

Appendix 4

Qualitative study data

All data are anonymised; each participant was recognised by an allocated letter of the alphabet.

Data from the interviews with participants

The verbal data from the interview transcripts were organised into themes. Emergent constructs are outlined and quotes from participants are presented to support each construct. Data are presented in *Tables 105–108*.

Comparison between those with constant and transient pain

Data for this comparison are given in *Tables 109* and *110*.

Influence of preference on outcome

Preference and effect data are given in *Table 111*.

TABLE 105 *Pain, activity and attitude to pain*

Effect of medication	Makes it worse No difference Limited help Major help Cure	"it just seems like I'm throwing stuff at it and nothing is happening" (K)
Duration and type of knee pain	Transient mild, moderate and severe Constant mild, moderate and severe	
Knee pain and other pain	Isolated knee pain Knee pain plus other musculoskeletal pain Knee pain plus other systemic problems	
Activity levels	Inactive – housebound Fairly inactive – active enough to survive independently Fairly active – functional active living plus additional lifestyle/hobby activity Active – functional activity plus busy lifestyle plus moderate voluntary engagement in physical activity Very active – active pursuit of additional physical exercise	"I do regular exercise (gives examples) to try and help my knee and generally keep my body in shape" (J) "err I do some voluntary work … that's about it really. I'm quite boring" (B) "I don't really go out, I stay in the house. That's just about it really"? (N) "Socialising and gardening and just general things and I try to walk as much as I can" (F) "I go to the gym three times a week … swimming … bit of walking"(G)
Attitude pain	Carry on regardless, best as can Carry on but at a much slower more careful place Positive and enabling modification and adaptation of behaviour, activity and lifestyle Negative and maladaptive modification of behaviour activity and lifestyle	"it makes me aware of what I'm doing, careful what I'm doing" (B) "it comes to a point of just having to stop and take a rest" (O) "its just steadily got worse (they said it would and it has)" (L) "I live with it … I don't let it get me down, I don't let it rule me" (L)

TABLE 106 *Preference*

Attitude to trial and allocation	Personal request to participate, feeling special Participation conditional on medication Extra attention and care for their pain	"I was just asked by (practice nurse) if I would just like to, you know, take it" (D)
Preference	Previous experience (personal or other) good and bad Perception of effectiveness Perception of risk Ease of use Curiosity Concept of preference by default (necessary medically)	"I hadn't tried the cream so I thought it would be interesting" (I) "well they seem to work" (O) "you can get addicted to things I think" (C)
Effect of previous experience	Personal – most powerful influence Family and friends – powerful influence Narratives – used to support opinion Previous illness – all relative to severity, e.g. knee pain to diabetes and heart failure Previous similar medication experience	"I've had stomach problems and I couldn't take the ibuprofen" (B) "I've never had any trouble taking tablets (heart, blood pressure); tablets have never been a problem to me" (G) (good experience) "I think long term in larger doses I think there would be risks" (O)
Reasons for doing trial	Personal request Curiosity Attention Help self Help others Speed healing process up	"I think they knew of me .... I'm a good guinea pig perhaps" (H) "it was a worthwhile project ... if I could contribute then I ought to do" (O)
Side-effects	None Heartburn Inconvenience (gel messy, takes time) Constipation Sickness Oesophagitis	"if I took ibuprofen every day, I'd have heartburn every day" (H) "I'm not normally a sicky person .... so I thought I would give things a rest just for a few days" (M)
Future	Resignation nothing of any use – avoidance Acceptable form of control – continue use Need more relief – use both Last resort – surgical intervention Exercise – self-help Alternative treatment	"I stand a lot, because I'm frightened I'll seize up" (M) "ah well, life goes on" (E) "I would try resting, then gel, then ibuprofen, then GP then knee replacement" (J) "New knees are a last resort" (A)

TABLE 107 *Knowledge*

Sources of information	Word of mouth – medical personnel – pharmacist – friends, family anyone Test results, X-rays Leaflets Magazines Adverts Rarely information sheet Internet (Inherent expectation of adverse effect)	"I'm squeamish about reading about side-effects because I imagine you have them later"(D) "eerr friends who sort of recommend things they've taken that are effective"(L) "she gave me leaflets ... books I've read .... adverts in the paper... I've listened to them (people) (M)

continued

TABLE 107 *Knowledge (cont'd)*

Trust in information	Medical staff superior knowledge Little trust in own knowledge Accept at face value narratives, no matter who from, no evaluation of knowledge and 'blind faith'	"no, just an ordinary laymen of the street, you know like you do when you're talking on the bus" (M) "If it was a doctor who said 'we'll try you on so and so', I would try it" (G)
Concepts and causes of pain	**Concepts** Swelling associated with pain but not a cause Inflammation is a poorly understood term and rarely used in lay circles Arthritis is seen as a diagnosis, cause and explanation Degeneration and weakness different Genetic inevitability **Causes** Loss of cartilage, bits missing, loss of cushioning Bones rubbing together Muscle deterioration weakness Previous injury, over use surgery Age, rotting, weight and pressure, cold, heat, gout Pain in other areas	"How does it know to go to your knee?" (D) I have no idea how they work (H, L, N) "It kills pain, it's not a cure" (B) "It does something to the brain that makes you think your not having pain" (M) The gel lubricates the joint (C) "It's in the mind too, the brain takes it to the parts that hurt" (E) "… get a walnut … . there's a nut inside, rotten … on the outside perfect" (K) "pain is caused by the cartilage disappearing" (so the natural padding goes causing the pain) "I assume it's the end of the bones rubbing together" (I) "the bones wear and crunch against one another" (B)
Action of medication	Very little understanding present Gel is absorbed through the skin into knee (blood, muscles, joint) to deaden pain. Effect local only Gel is absorbed and lubricates the knee Tablets go into the blood via the stomach, drugs travels around body to the knee to deaden the pain via the nerves Tablets go into the blood and to the brain telling the brain to stop recognising the pain No concept of anti-inflammatory action. Refer to drug as ibuleve or ibuprofen, pain killers or knee tablets	"… . makes the muscles swell and stops the joints rubbing together" (PH) "it's absorbed … . it's some sort of painkiller isn't it?" (A) "I feel as though something's been put back … like when you take fluid from something and you put fluid back" (M)
Beliefs	**Gel** Locally application makes it: faster acting, more specific/effective, less toxic to rest of the body Quicker the gel is absorbed the faster acting it is Gel not as strong as tablets because it doesn't have to go everywhere and be diluted **Tablets** Tablets are more toxic than gel Tablets go everywhere regardless Brain directs tablets to knee All over effect is positive, for those with multi-site Different medication for different pain sites	"It absorbed more easily so it had a faster effect"(D) "I think the cream just does your knee and the tablets go right through you" (better effect) (N) "you build up a tolerance to the tablets and then you have to go to something stronger" (B) "knee pain is nothing compared to my heart problems" (A)
Management	Concepts of levels of disability varied Ignore, accept, exercises to keep mobile and strong, rest, medication, oils, massage, movement, surgery, replacement, adaptation of behaviour to pre-empt problems, avoidance or modification	"I do make the effort … because if I don't I go very stiff" (M) "I do exercises to strengthen my knees every day" (C) "I just put up with it, I don't do anything with it" (F) "I cope by knowing my limitations and pre empting problems" (O)

TABLE 108 *Medication use*

Actual use	Only when pain present Every day for prevention Pre-emptive when they know knee will become painful, e.g. after an activity More application or dosage for more pain Never taking the maximum allowance to have some medication in reserve for emergencies, i.e. more severe pain	"mornings and evenings … I know it won't cure the problem but it's probably killing the pain" (C) "Only when I've got severe pain" (H) "Tablets, three times a day to help stem the pain" (G)
Understanding/ confusion	Mixed advice from trial staff and instructions leaflet Learning by trial and error what is best for themselves	"anything external is not so likely to get into the system" (yet effective?) (F)
Reasons for compliance and non-compliance	**Non-compliance** No swelling No pain Other problems worse Other medication better No effect Side-effects Inconvenient **Compliance** Allows for greater activity and less pain Cumulative effect Continual assessment in trial and visits Specially selected/responsibility Pain relief	**Passive compliance** "it starts to become part of your daily routine" (L) **Active compliance** "the tablets are keeping the pain at bay" (A)
Rationale for treatment	Taking supplements complements NSAIDS, seen as non-toxic, harmless but active! Surgery seen as a long term solution, less toxic than drugs Personal responsibility for knee pain, due to direct feedback as result of activity Take drugs to avoid surgery, replace knees when too old rest of body falling apart so no use	"No good having new knees if your body's falling apart is there? (M) "I take sleeping pills for the night" (N) "I use deep heat you can feel it doing something compared to the gel which does nothing" (K) "I use a walking stick in case it gives way" (M)
Influence of other pain	Knee pain insignificant to systemic illness Commonly associated with hip, back and ankle pain	"(her corns) maybe because it's like, made me walk funny" (K) "I know to pick up a reasonable weight, you bend your knees … with the arthritis … I do that less … . I'm fairly sure that's exacerbated a back problem" (I)
Use of other treatments	General view, mechanistic, well-oiled moving joints will do best Dog oil Glucosamine Cod liver oil, fish oils Exercise, walking aids Deep heat Sleeping tablets Quinine (cramps) Cortisone	"its like the tubi-sock and the heat pad … you can feel it" (K) (glucosamine) "more of a well being thing" (H) "somebody recommended to get some … dog oil" (G)

TABLE 109 *Constant pain*

Person	Type of pain	Drug and effect	Activity level	Beliefs	Causes of pain	Action of drugs	Actual use
A	Moderate	Gel Major help	Fairly inactive	Different pain needs different treatment	Degeneration	Anti-inflammatory. Low dose so no damage	Regular 3× per day
B	Moderate	Gel Cure	Fairly active	Build-up of tolerance to tablets	Bones rubbing and age	Kills pain not a cure, gel does not affect the stomach	Regular 3× per day
C	Severe	Gel Major help	Fairly active	Family support important. Needs a reserve so never takes full amount. Tablets are harmful	Bones rubbing and loss of cartilage	Gel lubricates the joint and calms the nerves	Regular 1× per day
D	Moderate	Gel Limited help	Fairly inactive	Gel gets to pain quicker, medication part of life	Friction, wear and tear	Local effect on nerves	When painful
E	Moderate	Gel Limited help	Very active	Over-use, cartilage and joints not working properly	Pinched cartilage, bone	Brain tells the drug where to work	When painful
F	Moderate	Tablets No difference	Fairly active	Trust in GP knowledge, as more than own	Wear and tear, loss of lubricant in knee	Local relief so message to brain saying there is no pain	Regular 2× per day

TABLE 110 *Transient pain*

Person	Type of pain	Drug and effect	Activity level	Beliefs	Causes of pain	Action of drugs	Actual use
G	Mild	Gel Limited help	Very active	Cold, wet weather affects the pain	Swelling	Relieves pain but has a cumulative effect	When painful
H	Moderate	Tablets Major help	Fairly inactive	Tablets are a short-term solution, sees oils as beneficial and longer-term help	Bones rubbing together due to missing cartilage	Has no idea	When painful
I	Moderate	Gel No difference	Fairly active	Different pain means different things	Swelling and bones rubbing and loss of cartilage	More medication means more pain relief	When painful
J	Mild	Gel No difference	Active	Pain not really bad enough to warrant treatment	Cartilage and bone	Anaesthetic effect	Regular then stopped because it made no difference
K	Severe	Tablets Made worse	Fairly inactive	Cold, wet weather makes it worse	Muscle deterioration and rotting bone	No idea	Regular then stopped due to side-effects
L	Severe	Tablets Major help	Fairly active	The cold wet weather makes it worse, moving and exercise important	Weakness and previous surgery	Local relief allowing better movement	Regular 3× per day
M	Moderate	Tablets Major help	Active	Weight makes it worse Keeps moving to keep knee working in case it stops	Weight, bones and lack of fluid in the knee	Drug travels to brain to stop pain messages	Regular 3× per day
N	Mild	Tablets Major help	Very active	Movement helps	Weight and aging	No idea, but has all over effect which is good	Regular 2× per day plus extra for gym sessions
O	Moderate	Tablets Major help	Fairly active	Long-term build-up poisoning the body	Movement causing friction and wear and tear	Local effect on the nerves	When painful

TABLE 111 *Preference and effect*

Person	Study	Preference	Preference met or not	Effect	Future choice
G	PPS	Gel, got gel	Met	Major help	Gel
C	PPS	No preference, chose gel	Met	Major help	Tablets or gel
I	PPS	Gel, got gel	Met	No difference	Tablets
J	PPS	Gel, got gel	Met	Limited help	Gel and tablets
A	PPS	Gel, got gel	Met	Major help	Gel
B	PPS	Gel, got gel	Met	Cure	Gel
H	RCT	Gel, or surgery got tablets	Not met	Major help (with surgery)	Gel or more surgery
K	RCT	Gel, got tablets	Not met	Made worse	Knee replacement
L	RCT	Tablets, got tablets	Met	Major help	Tablets and gel
M	RCT	Tablets, got tablets	Met	Major help	Tablets
N	RCT	Tablets, got tablets	Met	Major help	Tablets
O	RCT	Gel, got tablets	Not met	Major help	Gel or tablets
D	RCT	No preference, got gel	No preference	Limited help	Exercise
E	RCT	No preference, got gel	No preference	Limited help	Gel
F	RCT	Gel, got tablets	Not met	No difference plus side-effects	Gel

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We look forward to hearing from you.

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