NCCHTA

21 August 2007

TOIB Protocol

1. Are topical or oral Ibuprofen equally effective for the treatment of chronic knee pain
Topical or Oral Ibuprofen (TOIB)

2. Planned Investigation

Overall Aim

To determine whether general practitioners should advise their older patients with chronic knee pain to use topical or oral NSAIDs

Research Objectives

- Effectiveness
  - To compare the effect on knee pain and disability of general practitioner's advice 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 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 the route of administration has upon the NHS, 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 side-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

Existing research

Osteoarthritis (OA) is a common condition particularly in older people[1]. Symptoms include chronic pain and reduced mobility. Accurately estimating the prevalence and health impact of osteoarthritis is difficult, as there is an imprecise relationship between the presence of radiological change and symptoms of pain and/or disability. Data from the Tecumseh study in the USA showed that, based on history, 30% of women and 17% of men aged over 65 had OA, and, based on examination, 41% for women 20% for men had OA[2]. Radiological evidence of OA is nearly universal in older people. Sixty per cent of them will have moderate, or severe OA, in at least one joint[3]. However only 60% of x-ray changes are associated with symptoms [4] [5] [6]. The proportion of the UK population aged over 65 years is set to increase to one fifth by 2021 and there is evidence to suggest that age corrected consultation rates for osteoarthritis are also increasing[7]. Thus managing OA, particularly knee OA, is set to become an even more important health challenge over coming decades[8]. Community studies suggest that around 20-30% of those aged over 65 suffer from chronic knee pain[9] [10]. The vast majority of these patients who seek care, receive it in primary care. Since the only treatment convincingly shown to slow progression of OA is surgery, primary care management should target pain and disability[11].

Several trials have shown oral non-steroidal anti-inflammatory drugs (NSAIDs) to be superior to placebo in the treatment of OA of the knee [12]. Despite the risks of gastro-intestinal side effects, renal insufficiency, hepatic toxicity, exacerbation of asthma, sodium retention, raised blood pressure and resistance to anti-hypertensive drugs[13] they are widely used for the symptomatic treatment of OA, and other chronic musculoskeletal pain in older people[14]. There are few data on the direct, indirect and intangible costs and cost offsets from using NSAIDs in older people. The personal and economic costs of managing adverse effects are however large. Some studies do report on the epidemiology of NSAID related adverse events. Studies in younger people suggest that NSAID users have a mean blood pressure 5 mm Hg higher than non-users. This could have a large health impact in older people, 12-15% of whom take both NSAIDs and anti-hypertensive drugs. A 5-6 mm Hg increase in diastolic blood pressure may be associated with a 67% increase in stroke risk[15]. Around 40% of hospital admissions with upper gastrointestinal bleeding, and 40%

of associated deaths in older people are related to NSAID use[16]. Selective Cox II inhibitors may reduce gastrointestinal side complications, but with an annual incremental cost to the NHS drug budget of £25 million[17]. The magnitude of this reduction in gastrointestinal side effects may be no greater than the difference between low dose ibuprofen and other NSAIDs. Some COX-II inhibitors may increase cardiovascular risk[18]. Routine substitution of COX-II inhibitors for NSAIDs in older people is not justified on current evidence.
An alternative to using oral NSAIDs is to use topical NSAIDs which may have fewer side effects as a result of lower serum concentrations[19]. There are data to show that topical applications of Ibuprofen achieve therapeutic concentrations in deep compartments[20]. A meta-analysis of studies using topical NSAIDs for a range of chronic disorders concluded that they were more effective than placebo ointments[21]. However, there was some evidence of publication bias suggesting effect sizes might have been overestimated. The two studies identified that compared oral with topical NSAIDs for chronic disorders were of poor methodological standard and only used short-term outcome measures, 7 days[22] and 28 days[23]. The North of England Non-Steroidal Anti-Inflammatory Drug Guideline Development Group performed a review of published data coupled with expert knowledge and concluded that topical NSAIDs cannot be recommended as an evidence based treatment, and further highlighted the need for a trial comparing oral and topical drugs for osteoarthritis[24].

The continued popularity of rubefacients suggests that patients' responses to topical NSAIDs may be mediated partly through the act of rubbing the affected part, and by their beliefs about the mode of action when compared to oral medication as well as any pharmacological effect.
However, if the combined effect of

a) NSAID in the ointment, the act of rubbing, and the patients expectation of benefit produces an equivalent effect on pain and disability as oral NSAIDs **and**,
b) topical preparations have fewer adverse effects compared to oral preparations,

then topical medications may be preferable to oral ones for older patients with OA.
There remains a need for a trial to compare these two preparations on clinical grounds, before any cost considerations. However topical NSAIDs are considerably more expensive than oral preparations, for example 28 days supply of Ibuprofen 400mg three times daily basic NHS price is £2.44 and 100g of Ibuprofen gel (10%) is £6.50[13]. Considering that around 30% of the older population suffer from chronic knee pain and may benefit from such treatment there are large potential cost implications from using topical rather than oral NSAIDs. Such a trial must therefore include a robust health economic analysis that addresses the question;

Do possible reductions in costs of treating adverse events caused by NSAIDs' justify the increased cost of routinely advising topical preparations in preference to oral preparations?

There are compelling reasons for choosing chronic knee pain for a comparison of oral and topical Ibuprofen to test the effectiveness of oral or topical NSAID treatment for symptoms suggestive of OA:

- hip and knee OA are responsible for most of OA's health and social impact
- chronic knee OA is more common than chronic hip pain[9]
- different NSAIDs appear to be equally effective in the treatment of knee OA[25].
- a meta-analysis[26] and a large case control study[16] of the risk of gastro-intestinal side effects found that low dose ibuprofen had the lowest risk compared to other NSAIDs.
- The reduction in risk of gastrointestinal side effects between low dose oral ibuprofen and other NSAIDs or high dose ibuprofen is similar to that obtained by using COX-II inhibitors.
- ibuprofen is widely used both orally and topically for the treatment of osteoarthritis.
- most chronic knee pain is thought to be secondary to osteoarthritis[27]. There are problems in diagnosing OA, in that many older people have x-ray changes of OA without experiencing symptoms and even when x-ray changes are present OA may not be the cause of their pain.
- x-ray evidence of OA has little impact on pragmatic general practice management of knee pain in older people, indeed most such patients are treated without any x-rays being taken

TOIB will ascertain, if oral or topical Ibuprofen are equally effective at reducing pain and disability in people with chronic knee pain.

Research methods

A randomised controlled trial (RCT) with a parallel patient preference study (PPS) to

determine whether general practitioners should advise their older patients with chronic knee pain to use topical or oral NSAIDs

Since oral Ibuprofen is an established treatment, rather than seeking to show that topical Ibuprofen is either more, or less effective, than oral treatment, it is necessary to do an equivalence study. Such studies seek to 'define a range for the possible true difference between the treatments, any point of which is reasonably compatible with the observed data. If every point within this range corresponds to a difference of no clinical importance then the treatments may be considered to be equivalent'[28].
Rather than a trial that would answer the question, 'are the pain relieving properties of the two preparations equivalent', TOIB seeks to demonstrate that the patient outcomes are equivalent if general practitioners advise treatment with either topical or oral NSAIDs. This reflects the tendency for many patients with chronic knee pain to use treatments intermittently and to use both prescribed and over the counter medicines. At least one other trial is in progress comparing regular and as required analgesics for chronic knee pain (Carr A , personal communication). It is usual in equivalence studies to do an on-treatment analysis rather than an intention-to-treat analysis. However, as this study is 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 on-treatment analyses of the primary outcome measure and adverse effects will also be carried out.

RCTs are the least biased method for evaluating therapeutic interventions. Running a patient preference study alongside an RCT will considerably enhance the external validity of the study because,

a) The results of RCTs may not be generalisable if those with strong preferences for a particular treatment are excluded[29]. This is particularly a problem for treatment trials with physical components where it is impossible to blind participants to their allocation. Running a parallel PPS will allow such effects to be assessed.
b) The difficulties of recruiting trial participants from primary care are well known. Allowing those who are otherwise eligible who have a preference for a particular treatment to be recruited to a PPS will provide more observational data comparing two treatments. This was so successful in one recent trial that the preference arm was oversubscribed (it did also meet its randomisation target)[30]. Observational data from well-designed studies will often produce estimates of treatment effects similar to those of randomised controlled trials[31]. Data collected from the PPS will provide further information on relative efficacy of the two preparations.
c) An RCT is unlikely, on its own, to be large enough to identify any differences in serious adverse events. Including data collected from the PPS will provide further information on adverse events.

Additionally we will explore study participants' perceptions of treatment using depth interviews with a theoretical sample of participants from the pilot practices. This integration of qualitative data into the interpretation of the quantitative data may provide insights into any unexpected or anomalous findings[32 33].

Participants

The study will take place in 25 practices (plus 2 pilot practices) from the Medical Research Council General Practice Research Framework (GPRF)[34]. Practices selected will be nationally representative in terms of region, deprivation and type of locality (inner city/urban/sub-urban/rural).

Inclusion criteria

- aged 50 or over
- have had troublesome pain in or around the knee on most days for at least a month[10] **and** to have experienced knee pain for more than three months out of the preceding year[24].
- GP consultation, or treatment, for knee pain in the preceding three years.
- informed consent.
- agreement to use chosen or allocated treatment.
- GP agreement to prescribe oral/topical Ibuprofen.
- ability to complete postal questionnaires

Exclusion criteria

- peptic ulceration (past or current)
- current indigestion (on half or more days in the past three months)
- previous severe adverse reaction to NSAIDs
- severe hypertension
  (systolic BP of 155 mm of Hg or more **or** a diastolic BP of 95 mm of Hg or more.)
  (All potential participants with raised BP will be managed in accordance with usual practice policy)
- uncontrolled heart failure
- creatinine > 140 mmol/L
- abnormal liver function sufficient to contraindicate use of NSAIDs
- GP request not to include

- serious psychological or psychiatric disorders (including dementia)
- previous knee replacement/s or awaiting knee surgery
- inflammatory arthropathy
- serious injury within six months
- currently on anticoagulants
- anaemia (Hb <12.4 g/L for men or <11.8 g/L for women)
- disseminated malignancy

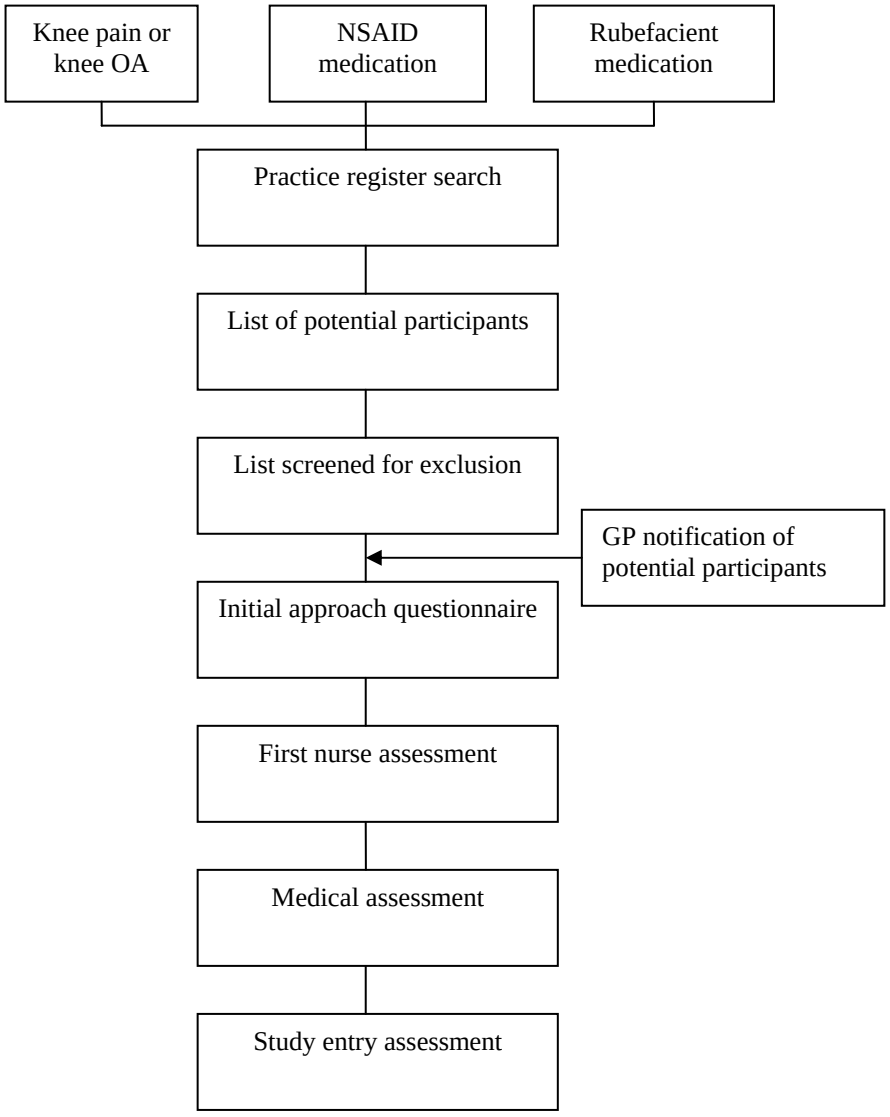
Participant identification and recruitment

In order to maximise recruitment three approaches will be used to identify potential participants:

a) Electronic medical records within general practices will be searched for patients aged 50 or over who have consulted with OA or knee/leg pain in the preceding 5 years.
b) Electronic prescribing databases will be searched for all patients aged 50 or over who have received a prescription for analgesic, oral/topical NSAIDs, or a rubefacient over the preceding year.
c) During the study recruitment period, GPs will be asked to notify the practice research nurse when potentially eligible patients consult.

In a trial using approach 'a' alone to identify participants comparing regular and 'as required' paracetamol for chronic knee pain only 10/300 (3%) people identified with OA from two GP surgeries agreed to be randomised (Carr A, personal communication). This low rate may be due to patients with well documented OA knee being reluctant to enter a study where the only treatment offered is paracetamol. A trial of arthritis self management (DASH) in patients aged over 55, in 17 GPRF practices used approaches 'a', 'b' & 'c', followed by medical record examination, to identify patients with a confirmed diagnosis of hip or knee osteoarthritis. Their most recent recruitment data found that 30% of patients, with confirmed OA who were approached were randomised. (Buszewicz M, personal communication).

Since potential participants identified in these three ways may be different, we will stratify randomisation according to practice, severity of pain and source of patient. Since practices are already responsible for treating patients from all three groups, overall the results will be generalisable to the routine clinical situation.



TOIB is a study of patients with chronic knee pain, a confirmed radiological or clinically diagnosis osteoarthritis is not needed. Given that; a) GP morbidity statistics[35] suggest that around 12% of those aged over 65 consult annually with osteoarthrosis and allied disorders. b) Data from a small pilot population survey, for a study of the epidemiology of knee pain, suggest that around 13% of those aged 55 or over consult annually with knee pain[24]. We can, conservatively, expect that the true contact rate with practices for knee pain older people is likely to be at least 10%. This means that a practice of 7,500 patients, 15% of which are aged 65 or over, will be in contact with 110 older people with knee pain each year. Based on the experience of the DASH trial, recruiting 20 of these (18%) of these to an RCT and a similar number to a PPS is a plausible recruitment target. Therefore we expect that 25 participating GPRF practices should be able to randomise a total of 275 participants to the RCT and recruit a further 368 participants to the PPS. Initial data suggest that participants to the PPS prefer topical treatment with a 3:1 ratio of topical to oral: for this reason more recruits to the preference study are needed.

Identification of potential participants

The practice based research nurses will perform a search on the practice computer to identify those who may have been in contact with the practice for knee pain in the previous five years. A search strategy that identifies possible OA/knee pain consultations/prescriptions has been used successfully for the DASH study (Buszewicz M, personal communication).

The output from this search will generate a comma-delimited file, on a floppy disc, summarising the patients' name and address data. The GPRF is developing a programme that uses this information to generate study ID numbers, personalised approach letters and all the necessary study paperwork that will be tested in a current study (BEXS study). A laptop containing the programme will be sent to each practice with a printer and pre-printed invitation letters, on which each potential participant's name and address can be added. To maintain confidentiality of patient specific data the practice nurse will run the programme on this computer with the trial clinician visiting to give help if required.

Invitations to participate, trial information sheets, questionnaires to screen for eligibility and expression of interest forms will be sent from and returned to the practice. The practice based research nurse will contact interested patients who appear eligible by telephone to confirm eligibility before inviting them for an initial assessment where trial procedures will be explained. Those who are eligible and interested will return for a baseline assessment one –two weeks later. The assessment procedures will be similar for patients in the RCT and PPS.

Initial assessment

Research nurse will 1) explain trial to the patient, 2) confirm eligibility, 3) measure blood pressure, peak expiratory flow rate, height and weight, 4) collect blood for full blood count, renal function, liver function tests and ferritin. Data will be collected on previous treatments (prescribed/over the counter medications and other treatments) expressed treatment preferences, and social class. Patients who otherwise appear eligible but who are unable to attend the surgery will be visited at home. Patients who are interested in participating will be asked not to use any topical or oral NSAIDs for one week before baseline assessment.

Diagnosis of osteoarthritis

To meet the American College of Rheumatologist's clinical criteria for osteoarthritis of the knee patients need to have knee pain, as defined for this study, and meet three out of the following six criteria:

- aged over fifty,
- less than 30 minutes morning stiffness,
- crepitus,
- bony tenderness,
- bony enlargement,
- no palpable warmth.

Measuring the proportion meeting these criteria will allow us to describe our sample more accurately and assess whether meeting these criteria affects outcome. Before potential participants attend for a baseline assessment they will be briefly assessed by a general practitioner to ascertain presence or absence of crepitus, bony tenderness, bony enlargement and palpable warmth. At this time we will ask them to assess the suitability of this patient and provide their agreement that they will be willing to prescribe either oral or topical ibuprofen for this potential participant.

Baseline assessment

Eligible and interested patients will return one to two weeks later to complete baseline questionnaires (see outcome measures) and to complete consent forms. Patients who are ineligible because of raised blood pressure or abnormal blood test results will be managed according to usual practice policy. Once treated those initially excluded because of severe hypertension will be eligible. Immediately after baseline assessment, those consenting to join the RCT will be randomised.

Allocation and protection from bias

We will, as far as possible, keep the main study team blind to participant's chosen/allocated treatment. A remote telephone randomisation service separate from the main study team will be used. On completion of the baseline assessment for patients consenting to either the RCT or the PPS, the nurse will phone the randomisation service with patient details. For those joining the RCT the randomisation service will use computer based randomisation to allocate treatment groups. Randomisation will be stratified by practice, severity of pain and source of patient. The randomisation service will confirm that entrants to RCT and PPS meet all the eligibility criteria. They will act as a repository for the participant's treatment choice/allocation. Thus, the central study team will be blinded to participants' treatment choice/allocation. Data on adherence with chosen/allocated treatment will be converted, in a blinded manner, into either a defined daily dose for medical record data, or an ordinal scale for questionnaire data, before the main analyses are carried out. These data will be used to assess adherence with chosen/randomised treatment. Only when follow up data are complete will the trial statistician, who will not have been involved in the data collection, receive information from the randomisation service on treatment allocations.

At a practice level the study will be open. This is necessary as both the practice and the participant will know which treatment arm they are in. The main outcome measures are all based on self-completed questionnaires; the only clinical outcomes measured by the practice research nurses are the participants' blood pressure and respiratory function. To avoid any bias from using conventional sphygmomanometers and peak flow meters, and ensuring accuracy of measurement, each practice will be provided with 1) a 'Dynomap', an electronic sphygmomanometer that relies on detecting intra-arterial vibrations for baseline and follow up blood pressure readings, and 2) an electronic peak flow meter. Unbiased mortality data will be collected from NHS central registry. Prescribing, selected diagnostic and hospital admission data will be collected from patient records by practice nurses. There is a potential for such data extraction to be biased. We cannot exclude the possibility of bias in how the data are entered into the medical record in an open study of this nature. All hospital admission letters will be anonymised and checked by clinical members of the study team for coding of admissions during follow up.

Pilot

This trial builds on the GPRF's considerable expertise in performing studies in primary care. The study team has particular expertise in identifying participants for studies of musculoskeletal problems in primary care. In particular the participant recruitment procedures build on the successful recruitment to the UK BEAM trial (1,350 randomised participants with back pain). The procedures for computerised generation of approach letters, and other paperwork, are being evaluated and refined in another study of chronic musculoskeletal pain running in the GPRF (BEXS). However, it essential that further piloting work is performed. In addition to the 25 practices for the main study it is proposed to pilot the study in two additional, GPRF practices in contrasting localities, making a total of 27 practices. This will allow us to test the recruitment and follow up procedures, to confirm that the estimated recruitment rate is achievable and to ensure acceptability of the postal questionnaires. In order to facilitate the qualitative study these will be in South East England.

Interventions, treatment, control

The two interventions being compared are the GP's recommendation (either a prescription or advice to get an over the counter preparation) to use either topical or oral Ibuprofen. The results of this trial will be used to inform general practitioners how to manage their older patients with knee pain and specifically whether they should advise/prescribe oral or topical NSAIDs. Thus for the comparisons to be meaningful they should reflect as closely as possible what happens in practice. Immediately after they have entered into the RCT or PPS participants will be provided with a supply of their chosen/allocated treatment by the research nurse. Subsequent supplies of their chosen/allocated treatment will be supplied, and monitored, through the practices' usual systems. Participants will be provided with an information sheet explaining the trial to give to any doctors who may treat them, and a laminated credit card summary that they can carry with them. Information about the trial will be placed in the practice records. Both the paper/electronic records and the prescribing database will be flagged to identify them as a trial patient. All of these information sources will ask those who treat the patient to use the chosen/allocated presentation of Ibuprofen as NSAID of choice for knee pain and other painful musculoskeletal conditions and to notify the study team of any serious potential adverse events. For those whose chosen/allocated treatment is oral ibuprofen, practices will be asked to use no more than 1.2g per day. Treatments for knee pain other than NSAIDs can be used as their doctor feels they are required. If a change of NSAID is needed they will be asked to use an alternative topical or oral presentation in line with trial treatment allocation (i.e. oral or topical). We will ask practices and patients to respect the treatment choices/allocations. However, if a change of treatment from topical to oral, or vice versa is considered essential by the GP, and patient, they can do this at their discretion. Essentially the practices are being asked to deliver two alternative versions of 'usual' general practice care

to trial participants. In the UK BEAM trial, GPRF practices were asked to provide a broadly defined package of usual care for control patients in a trial of manipulation and exercise for back pain. This approach worked well. We do not foresee major problems with asking practices to deliver two alternative versions of usual care for participants in this trial.

Adherence

Adherence with chosen/allocated treatment will be assessed using

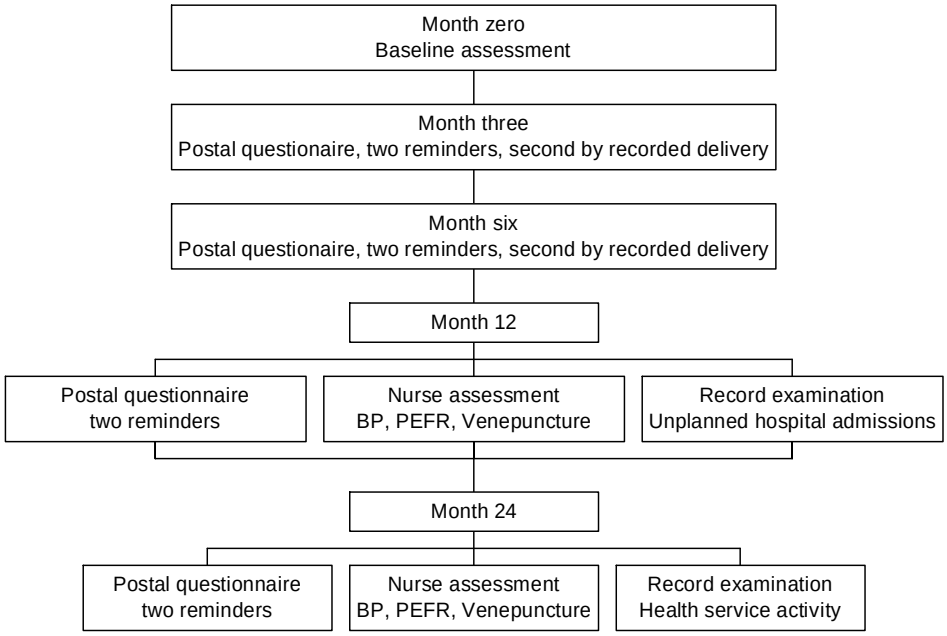
1. A summary of GP prescriptions issued for the trial participants, converted into Defined Daily Doses for topical/oral Ibuprofen and other topical/oral NSAIDs
2. Participant self report of the number of times they have purchased pain killing tablets or rubbing ointments over the counter.

In contrast to trials seeking to show a difference, analysed on an intention to treat (ITT) basis where poor adherence will tend to dilute any effect, in equivalence trials poor adherence to the allocated treatment regimen will tend to make it more likely that a wrong conclusion of equivalence is made. For this reason it is necessary to collect the data required to do a 'per protocol' (PP) analysis[25]. Unusually for an equivalence trial we are comparing two pragmatic interventions. An 'a priori' definition of which patients have received the essentials of treatment is needed to decide who to include in a PP analysis. *Participants will be considered to have received the essentials of treatment if the number of Defined Daily Doses of their chosen/allocated treatment prescribed by the practice is greater than the alternate treatment.*

Follow up

Follow up will be organised centrally. Postal questionnaires will consist of the same package of instruments collected at baseline. Participants will be sent postal questionnaires three, six, 12 and 24 months after randomisation. One year and two years after randomisation participants will be asked to visit the practice to have their blood pressure measured, peak expiratory flow rate measured and blood taken. The medical records will be examined, one year after randomisation to identify unplanned hospital admissions, and at the end of follow up to collect health service activity data. (see flow chart)

Follow up procedures



We will take the following steps to keep loss to follow up to a minimum:

1. There will be two reminders for each follow up questionnaire, the second by recorded delivery.
2. Participants who are unable to attend surgery for annual follow up will be visited at home by the practice nurse.
3. Participants will be flagged/traced at NHS central registry to ensure that we identify all deaths, and changes of general practitioner. This will also allow us to locate participants who have moved house to send postal questionnaires. Subject to agreement by their new general practitioner, follow up assessments for patients who have moved locally can be performed by the practice research nurse. For those who have moved further away where possible, we will, arrange for assessment to be performed by GPRF regional training nurses or the trial clinician.

Using less intensive follow up procedures than this, the UK BEAM study achieved 75% follow up after one year. We expect that a similar rate will be obtained for main outcome measures collected by post one year after randomisation and 67% two years after randomisation.

Qualitative study.

Initial depth interviews will be conducted, by a researcher experienced in social scientific methodologies during the first year after recruitment to the RCT and PPS .

Informants will be selected based on their age, severity of pain, treatment choice/allocation and occurrence of adverse events. To avoid any possibility that the interviews could, themselves, affect the participant's responses to the main outcome measures participants in the pilot study, whose data will not be included in the main analysis, will be interviewed soon after study entry. Any participants interviewed in study practices will be interviewed after the main study outcomes have been recorded at 1 year follow up.

Prior to the interviews the topic guide will be developed using a four-stage model.

- Brainstorming: Study team members will independently draw up list of possible questions and topic areas pertinent to the sub study's objectives
- Phrasing and sequencing: Study team meets to decide general flow of questions.
- Estimating time for questions: We aim to address 12 questions, of varying type, complexity and category. Though flexible, we anticipate the interviews lasting no more than two hours.
- Getting feedback from others and testing questions: Pilot topic guide will be tested on experienced qualitative researchers and healthcare professionals – and critical comments elicited .

Five categories of questions will be employed:

- Opening questions to help participants to feel comfortable with the interview
- Introductory questions which introduce the topic of discussion and stimulate subjects to reflect on their relationship to the topic of the study
- Transition questions that move the conversation into the key questions, which drive the study, logically linking the introductory questions and key questions.
- Key questions which drive the study. These take up more time and typically require pauses and probes for further depth.
- Ending questions bring closure to the discussion and enable participants to reflect on previous comments.

The questioning route will be developed in a similar manner to that used for the focus groups. It will be modified in the light of the findings from the initial interviews

Data management and validation

Validation: Data validity will be checked in the manner described by Polit and Hunger[36].

1. Data Source Triangulation: Using data from a range of professionals and patients.
2. Investigator Triangulation: A second researcher will examine a fifth of the transcripts. A proportion will also be examined by an outside researcher to scrutinise the grouping of narrative into themes and categories.
3. Member checks: A proportion of participants and health professionals experienced in working with older people with knee pain will be asked to comment on the researchers' interpretations.
4. Participant selection: Participants will be selected in a transparent manner from all those entering the study.
5. Participant feed back: Once all data are analysed and working papers are completed, the investigators intend to feedback to research participants a digest of findings.
6. Audit trail. A clear audit trail, that includes analytical procedures, will be open to independent inspection.

The data will first be presented by charting, this involves the development of themes extracted from the transcripts. This forms a useful standpoint from which to develop a theoretical analysis of the data. Data collected will be organised around themes, and particular attention paid to discordant voices or dissonant cases i.e. elements of the transcript that do not readily accommodate a theme but which are notable for future analysis.

Analysis

Data analysis will be developed along principles outlined by Harding and Gantley[37], i.e.

Transcribed data ➔ charted for emergent themes ➔ exploration and explanation of themes using analytical concepts

The validated themes will form the basis of a theoretical analytical interpretation. The interpretative theoretical context will be drawn from an established body of sociological knowledge on three substantive issues:

1. The 'reflexive self'[38], an individual whose interpretation of their condition may be developed, not purely from a blind acceptance of 'medical' knowledge but also from alternative informational sources, or their own illness experience.
2. The cultural construction of health risk[39], interactions with health personnel characterised as consumer – service provider, patient - professional.
3. The emergent role of patients as health service consumers[40]. The concept of risk[41] and the expectation on individuals to assess the risks to their health will also be applied to the transcripts of both patients and professionals. How individual patients articulate their perceived consequences of their choice of treatment will be explored.

However, a consumerist/provider model is increasingly replacing the traditional paternalistic model of the therapist/patient relationship. Thus, the traditional deferential therapeutic relationship has given way to a concept of the patient as a discerning health care consumer. Accompanying this has emerged the concept of the patient as 'expert'[42]. The difference between the 'expert' patient/consumer and the therapist 'expert' is that the knowledge base of the latter is credentiated in order to authenticate and distinguish it from that of the 'lay' population.

Risks vs benefits for participants and society,

Participant recruitment is dependent on being able to identify those with chronic knee pain from practice registers. We have designed systems for participant identification that ensure that all patient specific data are accessed only by practice staff, unless there is explicit consent to release this to the study team, ensuring that patient autonomy and confidentiality are respected.

There are well-documented risks of serious side effect from both oral and topical NSAIDs. Comparing these risks is, in part, why this trial is needed. All the participants are patients who, if the trial were not taking place, would be using, or be likely to use, either oral or topical NSAIDs. We do not expect the risk of participants suffering any adverse reaction to treatment to be any higher than if the trial was not taking place. Trial participants will have haemoglobin, renal function, pulmonary function and blood pressure monitored before and during the study, something that would not necessarily be usual practice, potentially reducing hazards to the participants. There will however be discomfort and a small risk of harm as a consequence of venepuncture. Since it is two versions of usual care that are being compared we do not expect any benefit to the participants from improved treatment. If the trial demonstrates that topical and oral NSAIDs are equally effective, and that topical NSAIDs have fewer adverse reactions then there are large potential benefits to society because of reduced treatment costs and improved quality of life for older people.

Consent,

Written consent will be obtained from all participants. Before this is obtained, participants will have had detailed information sheets, an initial assessment and opportunity to discuss the study with the practice research nurse and have had at least one week to consider their decision to participate. The research nurse will witness consent. Since we are comparing two versions of usual care, we do not think it necessary to have a third party to witness this consent.

Retention of trial documentation.

In line with MRC guidance, all documentation will be retained for 20 years after completion of the study.

Quality control

The practice based research nurses will all attend a training day in London to be instructed in the study procedures. They will also receive a detailed study manual. Practices will be instructed on study procedures, on site, by a member of the study team. GPRF regional training nurses will do two quality control visits, at times when potential/actual participants are being assessed, to each practice. One during recruitment and one during follow up. Both the study team and the GPRF regional training nurses will be available for advice and, if needed, practice visits.

Outcome measures

Data collection will be similar for the RCT and PPS

Efficacy

The primary clinical outcome measure will be the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire. It is a well established measure of both pain and disability used for OA knee[43] that is recommended as a standard outcome measure for knee OA trials. It has been reformulated to focus on knee pain rather than OA and tested using a postal questionnaire in a UK

population[24]. The WOMAC questionnaire measures pain and disability in the preceding 48 hours. Since the amount of pain and disability in this group is not constant, two longer term measures of pain and disability are included. The self reported disability scale used in the FAST trial of exercise for OA knee that covers the preceding month[44], and the postal version of the Chronic Pain Grade, that has been validated in a UK population,[45] that measures pain and disability over a preceding six month period will also be included. Two general measures of health status, the EQ5D a single index for describing and valuing health state produces a validated single measure of health status[46 47] and the SF-36[48] will be used. Additional questions assessing current health state as a measure of 'specific health transition'[49], and satisfaction with treatment will be included

Adverse effects

One year of follow up is adequate to decide if the two treatments are equally effective. Since many patients use these preparations for many years, adverse events will accrue over a longer period and prolonged follow up is needed. In the first instance, two years of follow up is proposed. A trial powered to show a difference in individual major adverse events would be implausibly large and major event monitoring is more appropriate for cohort or case control studies. For example, in the control arm of a trial of misoprostol for patients with rheumatoid arthritis taking NSAIDs 1% of patients had a serious upper gastrointestinal complication over six months[50]. If over two years the number of those in the oral treatment arm of this study with a documented upper gastrointestinal bleed was as high as 4%, to show that this was reduced by 50% in the topical treatment arm follow up data are needed from nearly 2,500 participants.

Furthermore ascribing causality for individual events to the medication will not usually be possible. For these reasons two composite measures of possible adverse effects from medication will be used.

Major possible adverse effects

The proportion who die or have an unplanned hospital admission. Deaths will be identified by practices when records are withdrawn and by flagging of records at NHS central registry. Unplanned hospital admissions will be identified from patient completed questionnaires, and annual medical record examination. Cause of admission will be ascertained from medical record. If necessary, the unplanned nature of an admission will be confirmed by the practice nurse contacting the participant. A similar approach worked well in the UK BEAM trial to identify those with potential adverse events following treatment.

Minor possible adverse effects

The composite measure of minor adverse events will be used to allow us to calculate the number needed to harm when comparing oral and topical medication. These possible adverse events might, in fact, be quite important for individual patients, however it is useful to designate these as 'minor' to distinguish them from death and hospital admission which are qualitatively more important. The external validity of this composite outcome measure is not known. During the lifetime of the trial, we will validate the items included in the measure by consulting with general practitioners using the Delphi technique to ensure that the most appropriate items have been included. We expect that a minor adverse event will be considered present if the participant has suffered one or more of the following:

- Iron deficiency or iron deficiency anaemia
  All participants found to have a ferritin of less than 12 μg/L or a haemoglobin of less than 12.4 g/L for men or 11.8 g/L for women either during routine clinical care, identified from medical records examination, or at annual assessment.
  Data from the Framingham study show that the prevalence of iron deficiency (2.7%), measured by serum ferritin, is over twice the prevalence of iron deficiency anaemia (1.2%) in a healthy elderly population[51]. Ferritin may therefore be a useful proxy for gastrointestinal bleeding. Mean difference in Hb and ferritin between baseline and follow up will also be presented with a 95% confidence interval
- New diagnosis of hypertension or failure of existing anti-hypertensive treatment or increase of 25 mm Hg in systolic or 15 mm Hg in diastolic blood pressure.
  NSAIDs have both a direct effect on blood pressure and make anti-hypertensive drugs less effective. New diagnoses of hypertension, requiring treatment with anti-hypertensive drugs and patients with hypertension who need a change of medication will be identified from the medical record examination.
- New diagnosis of asthma/chronic obstructive pulmonary disease (COPD), or a new prescription of either a beta-2 agonist or a steroid inhaler, or a 15% fall in peak flow.
  Explicit new diagnoses will be identified from the medical record. In a previous GPRF study (ELSAT) recording of new diagnoses of asthma in general practice record was found to be unreliable. For this reason the issue of a beta-2 agonist inhaler to someone who had not had one in the preceding year will be used as an indicator of a new diagnosis of asthma/COPD. Deterioration in asthma/COPD control will be considered present if a patient receives a steroid inhaler who had not had one in the year before randomisation. This approach will not identify all those whose lung function has been adversely affected; however it is a simple approach that will give an indication of numbers adversely affected.

- Renal impairment
  The upper limit of the normal range for creatinine in older people is 160mmol/L[52]. This is higher than a younger population. Patients with a creatinine >140mmol/L at baseline will not be included. Abnormal renal function will be considered present if there is a single reading of 160mmol/l or more found during routine clinical care, identified at annual record examination, or at annual assessment.
- Heart failure
  Few GPs have access to echocardiography to confirm the diagnosis of heart failure. For this reason any new diagnosis of heart failure in the practice records, with or without echocardiographic confirmation will be included.

As well as contributing to the composite minor adverse effects outcome measure the data from each of these events, and where appropriate their components, will also be reported

Health economic outcomes

We will look at the cost effectiveness of topical and oral Ibuprofen in terms of four key research questions:

1. What are the societal costs and benefits of implementing the programme, in terms of the impact the programme has upon the NHS, patient and other service providers?
2. What is the cost effectiveness of the programme over a two-year period and how is this influenced by treatment compliance?
3. What is the predicted long term cost effectiveness of the programme based on the likelihood and extent of major and minor side effects?
4. How do the elderly and their informal carers' value the time taken to seek medical advice and days off sick?

The incidence of serious adverse events caused by ibuprofen is such that a much larger trial is required to identify an important difference between the two groups. However these events, particularly hospital and nursing home admissions may have large financial and other costs. Particular care, therefore, will be made in measuring the financial impacts of side effects, even though they may be only a small number, to check if these affect the cost effectiveness result over the two year period.

Given that there is a band of 'uncertainty' around the measure of serious adverse events in this study we will conduct extensive sensitivity analysis around the cost effectiveness result, to check whether the result will be drastically altered under different estimates of serious adverse events.

Costs:

Costs will be obtained by recording units of resources used in both groups, and applying a tariff to each type of unit. Important resource units will be GP and practice nurse consultations, prescriptions and over-the-counter drug purchases, attendance at hospital accident and emergency departments, outpatients, and hospital bed-days. Health service usage will be based upon patients' self-reported usage, validated against medical records. Where possible, local cost tariffs will be used with national sources as comparator.

The costs to participants and their families will be obtained from the patient questionnaire and will include estimates of the time taken to seek medical advice. We are aware that the wage rate is unlikely to be an accurate measure of 'opportunity cost' for the elderly participants' time. Additionally, the patient questionnaire will record travel costs, home care costs and out of pocket expenses on additional drugs.

Quality of Life.

The participant questionnaire will collect two quality of life measures: a generic utility measure, the EQ5D, and a disease specific measure, WOMAC. We will ask participants to simply state their current health state along the five EQ5D dimensions and use this to categorise their health. We will not collect Time Trade Off or Standard Gamble values to derive a tariff for EQ5D states since other studies have shown difficulties in collecting this information for older populations concerning hip fractures. Instead, we will apply a tariff of EQ5D states derived in a national study[53].[54]. We feel this approach is feasible, given the success of other generic quality of life measures in older people[55] and Dempster's[56] work suggesting that older people can assess their functional ability.

Health economic analysis

The primary outcome measures for the economic component will be the WOMAC score for the cost effectiveness analysis and the EQ5D for the cost utility analysis. We will also compare the EQ5D measure against the WOMAC measure to check the extent to which the EQ5D is sensitive to quality of life changes. We will collect and analyse the health economic data in a conventional manner, using an incremental cost effectiveness ratio approach. We will conduct extensive 'sensitivity analysis' of our cost effectiveness result to the number of serious adverse events and rate of compliance. .

Sample size

Our sample size estimate was based on the primary efficacy measurement at one year. Previous work has shown that minimum differences in WOMAC pain and disability scales perceptible to patients are around 10-12mm on a 100mm visual analogue scale.[57] Typical standard deviations for the change between baseline and follow-up in knee OA trials are around 22mm. Our primary analysis will be the difference between groups in the change from baseline in WOMAC means score with 95% confidence intervals. To show a difference of 10mm with 90% power and 5% significance we needed analysable data on 103 subjects in each group. Assuming a 75% follow-up rate at one year, we needed to recruit 275 participants to the RCT. These numbers would show equivalence to within 10mm at 80% power.

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 to oral treatment in the PPS, and overall twice as many wanted to join the PPS as the RCT. These facts compromised the original sample size calculations. 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 10mm difference in WOMAC at the 5% level.

Analysis

It is usual in equivalence studies to do an on-treatment analysis rather than an intention-to-treat analysis. However, as this study is 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 on-treatment analyses of the primary outcome measure and adverse effects will also be carried out.

The primary outcome measure for efficacy will be the WOMAC pain score at one year. The change from baseline will be calculated for each participant and used as the dependent variable in the analysis. The baseline score, previous NSAID use, self medication, age, sex, and expectations for treatment may be used as a covariates in the analysis. The secondary outcome measures for efficacy are remaining WOMAC scores, FAST disability score, Chronic Pain Grade, EQ5D, GHQ-12, specific health transition, satisfaction with treatment and global judgements of 'troublesomeness' at three, six, 12 & 24 months.

There will be two primary outcomes for side effects, the composite measures of major and minor adverse events at two years. The secondary outcomes for adverse effects will be individual components of the composite outcome measures. All primary and secondary outcome measures will be tested for data quality and scaling assumptions prior to the main analysis. All significance tests will be two-sided.

Missing data will be handled two ways. Firstly, missing items within individual outcome measures will be treated according to the instructions for that measure. Secondly, the proportion of non-responders will be calculated for each treatment group and responders to the first questionnaire and to the first and second reminders will be compared.

Health economics

The primary outcome measures for the economic component will be the WOMAC score for the cost effectiveness analysis and the EQ5D for the cost utility analysis. We will also compare the EQ5D measure against the WOMAC measure to check the extent to which the EQ5D is sensitive to quality of life changes. The analysis will follow an incremental cost effectiveness ratio approach although the interpretation of negative cost effectiveness ratios can be problematic in modelling exercises[58]. Particular attention will be focused upon the variability of costs and outcomes data across different participant groups, and clinical settings. Confidence intervals will be set around the incremental cost effectiveness ratio of the programme, and will help to determine the extent to which our results can be generalised to other settings.

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