

# Pain reduction with oral methotrexate in knee osteoarthritis

<b>Submission date</b> 25/10/2013	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 25/10/2013	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 30/07/2024	<b>Condition category</b> Musculoskeletal Diseases	<input type="checkbox"/> Individual participant data

## Plain English Summary

### Background and study aims

Osteoarthritis (OA) is the most common form of arthritis and is an increasingly common problem in our aging society. In the UK an estimated 8.5 million people are affected by OA, causing an enormous burden to health authorities, as well as considerable pain and disability to these individuals. A recent study by Arthritis Care reported that 81% of people with OA experience constant pain and 72% have important related conditions, such as high blood pressure or depression. Current treatments for knee OA are limited as they often only work for short periods and are not effective for all patients. As a result people with OA often live with severe pain and have significant difficulty in carrying out their normal day-to-day activities. There is therefore an urgent need to find new and better ways to manage pain for people with OA. Methotrexate has been used very successfully to treat inflammation in rheumatoid arthritis, and it is now the drug used most often to treat that type of arthritis. Recent studies suggest that inflammation is also important in OA, and that by reducing inflammation, pain will also be reduced. The aim of this study is to find out whether methotrexate is an effective treatment for reducing inflammation in knee OA and whether this leads to a reduction in pain.

### Who can participate?

Patients aged 18 and over with knee OA

### What does the study involve?

Participants are randomly allocated to take either methotrexate or a placebo (dummy drug), in combination with drugs licensed for use in pain management of OA. Knee pain and function, pain in other joints, quality of life, anxiety, depression, and health service resource use are measured at the start of the study, and after 3, 6, 9 and 12 months.

### What are the possible benefits and risks of participating?

Not provided at time of registration

### Where is the study run from?

1. Leeds Teaching Hospitals Trust (UK)
2. Aintree University Hospital NHS Trust (UK)
3. Staffordshire and Stoke-on-Trent Partnership NHS Trust (UK)

4. Northumbria Healthcare NHS Foundation Trust (UK)
5. NHS Fife (UK)
6. Cannock Chase Hospital (UK)
7. New Cross Hospital (UK)
8. Guy's and St Thomas's NHS Foundation Trust (UK)
9. King's College Hospital (UK)
10. Ashford & St Peter's Hospitals NHS Foundation Trust (UK)
11. NIHR Wellcome Trust Southampton Clinical Research Facility (UK)
12. Harrogate and District NHS Foundation Trust (UK)
13. York Teaching Hospital NHS Foundation Trust (UK)
14. Salford Royal NHS Foundation Trust (UK)
15. Oxford University Hospitals NHS Foundation Trust (UK)
16. West Suffolk NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?  
January 2014 to January 2019

Who is funding the study?  
Arthritis Research UK

Who is the main contact?  
Sarah Kingsbury  
S.R.Kingsbury@leeds.ac.uk

## Contact information

**Type(s)**  
Scientific

**Contact name**  
Ms Sarah Kingsbury

**Contact details**  
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## Additional identifiers

**EudraCT/CTIS number**  
2013-001689-41

**IRAS number**

**ClinicalTrials.gov number**

## Secondary identifying numbers

15495

# Study information

## Scientific Title

Pain Reduction with Oral Methotrexate in knee Osteoarthritis: a pragmatic phase III trial of Treatment Effectiveness

## Acronym

PROMOTE

## Study hypothesis

Osteoarthritis (OA) is the most prevalent form of arthritis and is an increasingly common problem in our aging society. In the UK an estimated 8.5 million people are affected by OA, causing an enormous burden to health authorities, as well as considerable pain and disability to these individuals. A recent study by Arthritis Care reported that 81% of people with OA experience constant pain and 72% have important related conditions, such as hypertension or depression.

Current treatments for knee OA are limited as they often only work for short periods and are not effective for all patients. As a result people with OA often live with severe pain and have significant difficulty in carrying out their normal day-to-day activities. There is therefore an urgent need to find new and better ways to manage pain for people with OA. Methotrexate has been used very successfully to treat inflammation in rheumatoid arthritis; it is now the commonest drug used to treat that type of arthritis. Recent studies suggest that inflammation is also important in OA, and that by reducing inflammation, pain will also be reduced. The trialists believe that methotrexate may be an effective treatment for reducing inflammation in knee OA and that this reduction in inflammation will lead to a reduction in pain.

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

First MREC approval date 23/09/2013; 13/YH/0279

## Study design

Randomised interventional treatment trial

## Primary study design

Interventional

## Secondary study design

Randomised controlled trial

## Study setting(s)

Hospital

## Study type(s)

Treatment

## **Participant information sheet**

Not available in web format, please use contact details to request a participant information sheet

## **Condition**

Topic: Primary Care Research Network for England; Subtopic: Not Assigned; Disease: All Diseases

## **Interventions**

Patients will be randomised on a 1:1 basis to the intervention (Methotrexate, up to 25 mg per week) or placebo, used in combination with drugs licensed for use in pain management of OA

Follow Up Length: 13 months

## **Intervention Type**

Drug

## **Phase**

Phase III

## **Drug/device/biological/vaccine name(s)**

Methotrexate

## **Primary outcome measure**

Average overall knee pain severity over the 1-week period prior to measurement; Timepoint(s): 6 months

## **Secondary outcome measures**

Added 25/08/2016:

Clinical endpoints:

1. Patient-reported knee pain
2. Disease activity and knee function
3. Pain in other joints
4. Number of withdrawals due to total knee replacement in the signal knee

Measured at baseline, 3, 6, 9 and 12 months

Quality of life endpoints:

1. Quality of life
2. Anxiety and depression

Measured at baseline, 6 and 12 months

Resource use endpoints:

1. Health service resource utilisation
2. Imaging/MRI endpoints (MRI sub study)
3. Synovitis and cartilage scores

Measured at baseline, 6 and 12 months

## **Overall study start date**

01/01/2014

## **Overall study end date**

08/01/2019

## Eligibility

### Participant inclusion criteria

Current inclusion criteria as of 25/08/2016:

1. Fulfil clinical American College of Rheumatology (ACR) Criteria for knee OA
2. Knee pain on most days in the last 3 months
3. Insufficient pain relief from, inability to tolerate, or contra-indication to oral and/or topical Non-steroidal anti-inflammatory drugs (NSAIDs) and/or opioids and/or Paracetamol. Moderate to severe pain of the signal knee as defined by a score of  $\geq 40$ mm on a Visual analogue scale (VAS) (0-100mm) using the question "On average, how would you rate your knee pain during the last 3 months?"
4. Knee pain is the predominant pain condition
5. Patient able to identify a 'signal' painful knee (either the most painful knee or selected from equally painful knees)
6. A radiograph (X-Ray) of the signal knee within the last 2 years, with changes consistent with tibio-femoral OA
7. No change in the average weekly dose of oral/topical analgesics (including NSAIDs and Paracetamol) for at least 4 weeks
8. Has used chondroitin or glucosamine for at least 3 months with no change to the average weekly dose, is not using, or is willing to stop using if recently started
9. All male and female participants biologically capable of having children must agree to use a reliable method of contraception for the duration of the study and 24 weeks after the end of the study period. Acceptable methods of contraception are surgical sterilisation, oral, implantable or injectable hormonal methods, intrauterine devices or barrier contraceptives. If female and have potential for child bearing then a negative pregnancy test must be performed prior to starting treatment
10. The patient must be able to adhere to the study visit schedule and other protocol requirements
11. The patient must be capable of giving informed consent and the consent must be obtained prior to any screening procedures
12. All patients must have had a chest radiograph (X-Ray) within the last 6 months
13. Aged  $\geq 18$  years

Previous inclusion criteria:

1. Fulfil clinical ACR Criteria for knee OA.
2. Knee pain on most days in the last 3 months.
3. Insufficient pain relief from, inability to tolerate, or contra-indication to oral and/or topical NSAIDs and/or opioids. Moderate to severe pain of the signal knee as defined by a score of  $\geq 40$ mm on a VAS (0-100mm) using the question On average, how would you rate your knee pain during the last 3 months?.
4. Knee pain is the predominant pain condition.
5. Patient able to identify a signal painful knee (either the most painful knee or selected from equally painful knees).
6. A previous radiograph (X-Ray) of the signal knee with changes consistent with tibiofemoral OA.
7. No change in the average weekly dose of oral/topical analgesics (including NSAIDs) for at least 4 weeks.
8. Has used chondroitin or glucosamine for at least 3 months with no change to the average weekly dose, is not using or is willing to stop using if recently started.
9. Men and women must use adequate birth control measures (e.g. abstinence, oral

contraceptives, Intra-uterine device, barrier method with spermicide, or surgical sterilisation) for the duration of the study and should continue such precautions for 6 months after receiving the last dose of MTX. If female and have potential for child bearing then a negative pregnancy test must be performed prior to starting treatment.

10. The patient must be able to adhere to the study visit schedule and other protocol requirements.

11. The patient must be capable of giving informed consent and the consent must be obtained prior to any screening procedures.

12. All patients must have had a chest radiograph (X-Ray) within the last 6 months.

13. Target Gender: Male & Female ; Lower Age Limit 18 years

### **Participant type(s)**

Patient

### **Age group**

Adult

### **Lower age limit**

18 Years

### **Sex**

Both

### **Target number of participants**

UK Sample Size: 160

### **Total final enrolment**

155

### **Participant exclusion criteria**

Current exclusion criteria as of 25/08/2016:

1. The presence of any inflammatory arthritis (e.g. gout, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, seronegative spondylarthropathy, previous diagnosis of pseudogout in target joint with proven crystals on joint aspiration or elevated CRP at time of knee arthritis flare) or fibromyalgia.
2. Use of intra-articular (IA) hyaluronic acid in the signal knee within the 4 months preceding enrolment in the study.
3. Use of IA, IM or oral corticosteroids in the 3 months preceding enrolment.
4. Use of other anti-synovial agents (e.g. hydroxychloroquine or sulphasalazine) in the 2 months preceding the study.
5. Significant knee injury or any knee surgery within the 6 months preceding enrolment in the study.
6. A history of partial or complete joint replacement surgery in the signal knee at any time, listed for knee surgery, or anticipating knee surgery during the study period.
7. Commencement of physiotherapy or non-pharmacological knee OA treatment in the 2 months preceding the study.
8. The presence of non-OA causes of pain in the signal knee e.g. referred hip pain, osteonecrosis.
9. Women who are pregnant, breast-feeding, or men or women planning pregnancy within 18 months after screening (i.e. approximately 6 months following last study medications).
10. Use of any investigational (unlicensed) drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.

11. Have current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral disease, or active current infection.
12. Uncontrolled disease states, such as moderate/severe asthma, Chronic Obstructive Pulmonary Disease (COPD) or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids, or recurrent infections.
13. Unwilling to keep alcohol intake to below the recommended maximum daily limit during the trial (2 units per day for women, 3 units per day for men).
14. Planned need for live vaccination during 12 months of study (e.g. for foreign travel) with exception of Zostavax® which is permissible.
15. Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period.
16. Melanoma, squamous cell carcinoma or non-skin cancer in the past 3 years.
17. Intolerance to lactose.
18. Significant haematological or biochemical abnormality
  - 18.1. Haemoglobin = <8.5 g/dL
  - 18.2. WCC = <3.5 x 10<sup>9</sup>/L
  - 18.3. Neutrophils = <1.5 x 10<sup>9</sup>/L
  - 18.4. Platelets = <100 x 10<sup>9</sup>/L
  - 18.5. ALT >2 times ULN for the laboratory conducting the test.
  - 18.6. Creatinine > 1.5 times ULN for the laboratory conducting the test
  - 18.7. eGFR <30ml/minute

Subjects with the following contra-indications to MRI scanning will not be included in the MRI substudy but may still be enrolled into the main study:

1. Pacemakers
2. Surgical clips within the head
3. Certain inner ear implants
4. Neuro-electrical stimulators
5. Metal fragments within the eye or head

Previous exclusion criteria:

1. The presence of any inflammatory arthritis (e.g. gout, reactive arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, seronegative spondylarthropathy) or fibromyalgia.
2. Use of intra-articular (IA) hyaluronic acid in the signal knee within the 4 months preceding enrolment in the study.
3. Use of IA, IM or oral corticosteroids in the 3 months preceding enrolment.
4. Use of other anti-synovial agents (e.g. hydroxychloroquine or sulphasalazine) in the 2 months preceding the study.
5. Significant knee injury or any knee surgery within the 6 months preceding enrolment in the study.
6. A history of partial or complete joint replacement surgery in the signal knee at any time, listed for knee surgery or anticipating knee surgery during the study period.
7. Commencement of physiotherapy or non-pharmacological knee OA treatment in the 2 months preceding the study.
8. The presence of non-OA causes of pain in the signal knee e.g. referred hip pain, osteonecrosis.
9. Women who are pregnant, breast-feeding, or men or women planning pregnancy within 18 months after screening (i.e. approximately 6 months following last study medications).
10. Use of any investigational (unlicensed) drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.
11. Have current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease.

12. Uncontrolled disease states, such as moderate/severe asthma, COPD or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids, or recurrent infections.
13. Intake of alcohol above the recommended government guidelines (2 units per day for women, 3 units per day for men).
14. Planned need for live vaccination during 12 months of study (e.g. for foreign travel) or lack of immunity to chicken pox.
15. Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period.
16. Melanoma or non-skin cancer in the past 3 years.
17. Intolerance to lactose.
18. Significant haematological or biochemical abnormality
  - 18.1. Haemoglobin  $\leq$  8.5 g/dL
  - 18.2. WCC  $\leq$  3.5 x 10<sup>9</sup>/L
  - 18.3. Neutrophils  $\leq$  1.5 x 10<sup>9</sup>/L
  - 18.4. Platelets  $\leq$  100 x 10<sup>9</sup>/L
  - 18.5. ALT >2 times ULN for the laboratory conducting the test.
  - 18.6. Creatinine > 1.5 times ULN for the laboratory conducting the test
  - 18.7. eGFR <30ml/minute

Subjects with the following contra-indications to MRI scanning will not be included in the MRI substudy but may still be enrolled into the main study:

1. Pacemakers
2. Surgical clips within the head
3. Certain inner ear implants
4. Neuro-electrical stimulators
5. Metal fragments within the eye or head

**Recruitment start date**

01/05/2014

**Recruitment end date**

31/08/2016

## **Locations**

**Countries of recruitment**

England

Scotland

United Kingdom

**Study participating centre**

**Leeds Teaching Hospitals Trust**

Chapel Allerton Hospital

Chapeltown Road



Leeds  
United Kingdom  
LS7 4SA

**Study participating centre**  
**Aintree University Hospital NHS Trust**  
Longmoor Lane  
Liverpool  
United Kingdom  
L9 7AL

**Study participating centre**  
**Staffordshire and Stoke-on-Trent Partnership NHS Trust**  
Haywood Hospital  
High Lane  
Burslem  
Stoke-On-Trent  
United Kingdom  
ST6 7AG

**Study participating centre**  
**Northumbria Healthcare NHS Foundation Trust**  
Rake Lane  
North Shields  
United Kingdom  
NE29 8NH

**Study participating centre**  
**NHS Fife**  
Victoria Hospital  
Hayfield Road  
Kirkcaldy  
United Kingdom  
KY2 5AH

**Study participating centre**  
**Cannock Chase Hospital**  
Brunswick Road  
Cannock  
United Kingdom  
WS11 5XY

**Study participating centre**

**New Cross Hospital**

Wolverhampton Road

Wolverhampton

United Kingdom

WV10 0QP

**Study participating centre**

**Guys and St Thomas's**

Guy's Hospital

Great Maze Pond

London

United Kingdom

SE1 9RT

**Study participating centre**

**King's College Hospital**

King's College London

Suite 3, Golden Jubilee Wing

King's College Hospital

Denmark Hill

London

United Kingdom

SE5 9RS

**Study participating centre**

**Ashford & St Peter's Hospitals NHS Foundation Trust**

Guildford Road

Chertsey

United Kingdom

KT16 0PZ

**Study participating centre**

**NIHR Wellcome Trust Southampton Clinical Research Facility**

Southampton Centre for Biomedical Research

C Level West Wing

Mailpoint 218

Southampton General Hospital

Tremona Road

Southampton

United Kingdom  
SO16 6YD

**Study participating centre**

**Harrogate and District NHS Foundation Trust**  
Lancaster Park Road  
Harrogate  
York  
United Kingdom  
HG2 7SX

**Study participating centre**

**York Teaching Hospital NHS Foundation Trust**  
Wigginton Road  
York  
United Kingdom  
YO31 8HE

**Study participating centre**

**Salford Royal NHS Foundation Trust**  
Stott Lane  
Salford  
United Kingdom  
M6 8HD

**Study participating centre**

**Oxford University Hospitals NHS Foundation Trust**  
Nuffield Orthopaedic Centre  
Windmill Road  
Headington  
Oxford  
United Kingdom  
OX3 7HE

**Study participating centre**

**West Suffolk NHS Foundation Trust**  
Hardwick Lane  
Bury St Edmunds  
United Kingdom  
IP33 2QZ

# Sponsor information

## Organisation

University of Leeds (UK)

## Sponsor details

Faculty Research Office  
Room 10.110, Level 10 Worsley Building  
Clarendon Way  
Leeds  
England  
United Kingdom  
LS2 9NL

## Sponsor type

University/education

## Website

<http://www.leeds.ac.uk/>

## ROR

<https://ror.org/024mrx33>

# Funder(s)

## Funder type

Charity

## Funder Name

Arthritis Research UK (UK)

## Alternative Name(s)

## Funding Body Type

Private sector organisation

## Funding Body Subtype

Other non-profit organizations

## Location

United Kingdom

# Results and Publications

## Publication and dissemination plan

To be confirmed at a later date

## Intention to publish date

31/12/2019

## Individual participant data (IPD) sharing plan

Fully anonymised datasets generated during the current study will be available upon request from Prof. Torgerson (e-mail, david.torgerson@york.ac.uk).

## IPD sharing plan summary

Available on request

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Protocol article</a>	protocol	04/03/2015		Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Results article</a>		30/07/2024	30/07/2024	Yes	No