

# A randomized controlled trial of adalimumab injection plus physiotherapy compared with placebo plus physiotherapy for patients with sciatica

<b>Submission date</b> 12/12/2014	<b>Recruitment status</b> Stopped	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 15/12/2014	<b>Overall study status</b> Stopped	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 06/08/2018	<b>Condition category</b> Musculoskeletal Diseases	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Sciatica is defined as well-localised leg pain with a sharp, shooting or burning quality that normally radiates to the foot or ankle. Current treatment in the NHS typically involves the prescribing of analgesia (painkillers) by their general practitioner, and if troublesome symptoms continue, physiotherapy. If pain persists patients are referred for more invasive treatment such as corticosteroid injection and eventually surgery. Monoclonal antibody treatments (e.g. etanercept, infliximab, adalimumab) are increasingly used to control inflammatory disease. Although expensive, they may be cost-effective if they reduce the need for more expensive treatments such as surgery. The aim of this study is to find out how effective adalimumab injections plus physiotherapy are, compared with saline (placebo) injections plus physiotherapy, for patients with sciatica whose pain is troublesome and persistent despite treatment from their GP.

### Who can participate?

Adults 18 years or older with suspected sciatica who have failed primary care treatment. This will be defined as troublesome symptoms persisting for longer than four weeks, including patients whose symptoms settle but then recur, or earlier if they have severe uncontrolled pain.

### What does the study involve?

At the first assessment eligibility will be checked, the study explained fully, and initial consent obtained. Participants will then be registered onto the trial. Within two to three weeks of the first assessment visit the participant will be sent for a routine blood test, tuberculosis (TB) screening including a chest X-ray, counselling by a research nurse about adalimumab; and a magnetic resonance imaging (MRI) scan to exclude any serious spinal problem. After two to three weeks participants will need to attend a second assessment at the clinic to determine if they are still eligible and confirm that counselling, TB screening, MRI and blood tests have been performed and are satisfactory. At this visit three copies of a second informed consent form will be signed and participant will begin the study. They will also complete a questionnaire asking

about their sciatica pain and how it affects their health. Participants will be randomly allocated to one of two groups. One group will receive two injections of adalimumab followed by one injection two weeks later. The other group will receive the same number of saline (placebo) injections. The injections will be prescribed by a consultant rheumatologist and administered by a rheumatology specialist nurse experienced in the administration of these injections. The first injections will be given on the same day the participant attends the second assessment at the clinic. They will also be asked which group they think they are in, and given an appointment to return two weeks later for their last injection. Both groups will also attend a course of physiotherapy which will consist of a package of treatment including exercises designed for patients with sciatica. After participants complete the physiotherapy treatment, if their symptoms have settled they will be referred back to their GP; if their symptoms persist they will be referred by their physiotherapist for further treatment in the local spinal clinic.

Follow-up questionnaires will also be sent to the participants in the post after six weeks, six and twelve months. They will contain a free post envelope for them to return. Two weeks after the twelve month questionnaire has been sent they will be contacted by a member of the research team and asked about their overall experience of the study and follow-up treatment and also asking which treatment group they thought they were in.

What are the possible benefits and risks of participating?

The possible benefits are that participants will receive physiotherapy treatment in addition to the injections, for their sciatic pain. Physiotherapy is often used for patients with sciatica and there is evidence to suggest that it helps a number of them. We hope that participants will benefit from the physiotherapy treatment. We do not know whether participants will benefit from the injections, but we hope that the information we get from the study results will help to improve the treatment options for patients with sciatica. The adalimumab used in this trial has known side-effects, but we have a great deal of experience in using it safely for illnesses like rheumatoid arthritis. The most common side-effects are reactions at the injection site, such as redness, swelling or pain. These reactions aren't usually serious. Adalimumab affects the immune system (the body's own defence system), so participants may be more likely to develop infections. At the same time, adalimumab can mask the symptoms of infection so participants may not feel as ill as they might normally do with an infection.

Where is the study run from?

The study has been set up and is being co-ordinated by the North Wales Organisation for Randomised Trials in Health and Social Care (NWORTH), and participants will be referred from primary care involving five confirmed centres (North Wales, Keele, Nottingham, London, and Cardiff) and from secondary care physiotherapy outpatient clinics.

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

It is anticipated that recruitment will start in April 2015. Participants will be enrolled on the study for a period of two years.

Who is funding the study?

NIHR Health Technology Assessment Programme - HTA (UK).

Who is the main contact?

Dr Nefyn Williams (nefyn.williams@bangor.ac.uk)

Mrs Alison Jenkins (a.jenkins@bangor.ac.uk)

## Contact information

**Type(s)**

Scientific

**Contact name**

Dr Nefyn Williams

**Contact details**

North Wales Organisation for Randomised Trials in Health (NWORTH)

Y Wern

Normal Site

Holyhead Road

Bangor

United Kingdom

LL57 2DG

+44 (0)1248 383102

nefyn.williams@bangor.ac.uk

**Type(s)**

Public

**Contact name**

Mrs Alison Jenkins

**Contact details**

North Wales Organisation for Randomised Trials in Health (NWORTH)

Meirion Building

Normal Site

Holyhead Road

Bangor

United Kingdom

LL57 2DG

+44 (0)1248 382442

a.jenkins@bangor.ac.uk

**Additional identifiers****EudraCT/CTIS number**

2015-000636-15

**IRAS number****ClinicalTrials.gov number****Secondary identifying numbers**

HTA 12/201/02

**Study information****Scientific Title**

A randomized controlled trial of adalimumab injection compared with placebo for patients receiving physiotherapy treatment for sciatica

## **Acronym**

Subcutaneous Injection of Adalimumab Trial compared with Control (SCIATiC)

## **Study objectives**

Sciatica is a symptom defined as unilateral, well-localised leg pain, with a sharp, shooting or burning quality, that approximates to the dermatomal distribution of the sciatic nerve down the posterior lateral aspect of the leg, and normally radiates to the foot or ankle.

To evaluate the effectiveness of subcutaneous injections of adalimumab plus physiotherapy compared with placebo injection of 0.9% Sodium Chloride plus physiotherapy for patients with sciatica who have failed first-line primary care treatment. Potential participants will be identified during primary care consultation, musculoskeletal service or practice database search. The primary effectiveness outcome will be sciatica-related health status using the Oswestry Disability Index. Secondary effectiveness outcomes will include pain intensity, location, duration and anticipated trajectory; the risk of poor outcome; psychological measures including fear avoidance beliefs, self-efficacy, anxiety and depression; employment status; adverse effects.

To evaluate the cost-effectiveness of subcutaneous injections of adalimumab plus physiotherapy compared with placebo injection of 0.9% Sodium Chloride plus physiotherapy for patients with sciatica who have failed first-line primary care treatment from a health service and personal social care perspective. The primary economic outcome will be the incremental cost per Quality Adjusted Life Year (QALY) gained. QALYs will be estimated by administering the EQ-5D-5L at each follow-up visit.

More details can be found at: <http://www.nets.nihr.ac.uk/projects/hta/1220102>

Protocol can be found at: [http://www.nets.nihr.ac.uk/\\_\\_data/assets/pdf\\_file/0003/144561/PRO-12-201-02.pdf](http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0003/144561/PRO-12-201-02.pdf)

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

Wales REC 3, 27/05/2015, REC ref: 15/WA/0105

## **Study design**

Multi-centre randomised controlled trial and concurrent economic evaluation with internal pilot study

## **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 the contact details below to request a patient information sheet

**Health condition(s) or problem(s) studied**

Sciatica

**Interventions**

All participants will be randomised to receive two doses of subcutaneous injection two weeks apart. The intervention group will receive 80 mg adalimumab followed by 40 mg in order to administer a therapeutic dose of adalimumab for a period of four weeks. The control group will receive an equivalent volume of 0.9% Sodium Chloride. In this trial both groups will receive a concurrent course of physiotherapy intervention which can be described as 'best conservative care'. It will be delivered in local physiotherapy departments.

**Intervention Type**

Biological/Vaccine

**Primary outcome measure**

The primary clinical outcome will be back pain specific disability using the Oswestry Disability Index measured at 12 months.

The primary economic outcomes will be the incremental cost per QALY gained, estimated by administering the EQ-5D-5L at each follow-up visit.

**Secondary outcome measures**

Other outcomes will measure: physical function, generic health status, health utility, fear avoidance beliefs, self-efficacy, anxiety & depression, employment status, use of health and personal social care services, adverse events. Secondary continuous outcome variables will be assessed in a similar way to the primary outcome variable, with the exception of time to referral for surgery, which will be assessed from trial entry using Kaplan-Meier survival analyses and the log rank test. Dichotomous variables will be explored using logistic regression. These analyses will be repeated using pre-specified participant subgroups (including the presence of neurological deficit on entry to the trial and MRI findings).

An exploratory analysis will trial the association between the clinical symptoms and MRI findings will be assessed by two independent radiologists who will interpret the proximity of the affected nerve root and the disc bulge or extrusion, and the probability that the nerve root is irritated by other pathology such as spondylosis. The level of agreement between the radiologists will be demonstrated using the kappa statistic. Clinical and MRI findings will be included in analyses of treatment response and treatment interactions.

**Overall study start date**

01/01/2015

**Completion date**

30/06/2018

**Reason abandoned (if study stopped)**

Participant recruitment issue

# Eligibility

## Key inclusion criteria

1. 18 years of age and older
2. Clinical features of sciatica
3. Leg pain worse or as bad as back pain, obtained by asking the participant
4. Unilateral leg pain approximating a dermatomal distribution (contralateral buttock pain permitted if it does not extend below the inferior gluteal margin) obtained by asking the participant
5. One of the following:
  - 5.1. Positive neural tension test such as straight leg raise test (SLR) restricted <50 degrees by leg pain; positive femoral stretch test
  - 5.2. Muscle weakness or loss of tendon reflex affecting one myotome
  - 5.3. Loss of sensation in a dermatomal distribution
6. Persistent symptoms for at least 4 weeks and less than 6 months despite first-line treatment in primary care; obtained by asking the participant
7. Moderate to high severity ( $\geq 30$ ) on Oswestry Disability Index
8. Female partners of sexually active men should use adequate contraceptives for at least five months after the last injection. Female patients should have a negative urine pregnancy test within 2 weeks prior to randomisation, unless they are post-menopausal or have had a sterilisation operation. Sexually active men must also use adequate contraceptive methods

## Participant type(s)

Patient

## Age group

Adult

## Lower age limit

18 Years

## Sex

Both

## Target number of participants

332

## Key exclusion criteria

1. Symptoms persisting for longer than 6 months obtained by asking the participant
2. A previous episode of sciatica in the last 6 months
3. Unable to perform MRI (e.g., magnetic metal implants, potential metallic intra-ocular foreign bodies, claustrophobia, extreme obesity) obtained from the medical records and by asking the participant
4. Serious spinal pathology, including cauda equina syndrome, malignancy, recent fracture, infection or very large disc prolapse which might require an urgent spinal surgery opinion, identified from participants' previous medical history in their medical records or from magnetic resonance imaging (MRI)
5. Incidental serious pathology identified by MRI (e.g., adrenal tumour)
6. Neurological deficit involving muscle weakness requiring an urgent spinal surgery assessment e.g. foot drop

7. Widespread pain throughout the body including the upper limb (pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain [cervical spine or anterior chest or thoracic spine or low back] must be present)
8. Prior use of biological agents targeting TNF-alpha within the previous 6 months obtained from the medical records and by asking participant
9. Previous lumbar spinal surgery obtained from the medical records and by asking the participant
10. Contra-indications to adalimumab injection including serious infection such as active or latent tuberculosis, transplanted organ, demyelinating disorders, malignancy, cardiac failure, low white cell count, pregnancy obtained from the medical records, results of investigations and by asking the participant
11. Pregnant or breastfeeding (women must not breastfeed for at least 5 months after the last adalimumab injection)
12. Unable to communicate in English or Welsh; unable or unwilling to give informed consent

**Date of first enrolment**

01/04/2015

**Date of final enrolment**

01/11/2016

## **Locations**

**Countries of recruitment**

England

United Kingdom

Wales

**Study participating centre**

**North Wales Centre for Primary Care Research**

Bangor University

Gwenfro Unit 4

Wrexham Technology Park

Wrexham

United Kingdom

LL13 7YP

**Study participating centre**

**Keele University**

Arthritis Research UK Primary Care Centre

Primary Care Sciences

Keele University

Staffordshire  
United Kingdom  
ST5 5BG

**Study participating centre**  
**Sherwood Forest Hospitals NHS Trust**  
United Kingdom  
-

**Study participating centre**  
**Cardiff University**  
Cardiff  
United Kingdom  
CF10 3XQ

**Study participating centre**  
**Queen Mary University London**  
London  
United Kingdom  
E1 4NS

## **Sponsor information**

**Organisation**  
Bangor University (UK)

**Sponsor details**  
Schools of Healthcare and Medical Sciences  
Bangor University Fron Heulog  
Bangor  
Wales  
United Kingdom  
LL57 2EF  
+44 (0)1248 388451  
hss042@bangor.ac.uk

**Sponsor type**  
University/education

**ROR**  
<https://ror.org/006jb1a24>



# Funder(s)

## Funder type

Government

## Funder Name

Health Technology Assessment Programme

## Alternative Name(s)

NIHR Health Technology Assessment Programme, HTA

## Funding Body Type

Government organisation

## Funding Body Subtype

National government

## Location

United Kingdom

# Results and Publications

## Publication and dissemination plan

Results from this trial will be presented at regional national and international meetings where interested doctors, therapists, specialist nurses and health service commissioners would be present. This would include specialist meetings relating to musculoskeletal problems, orthopaedics, rheumatology, primary care and health economics.

In addition to preparing a monograph for the Health Technology series, papers will be submitted to relevant international journals such as Spine, Spine Journal, British Medical Journal, Lancet.

The results will be distributed to policy makers, advisory groups and professional bodies, for example the Welsh Government, the National Strategic Advisory Group (NSAG), and NICE.

Bangor University maintains information on a range of projects with the potential for commercial outputs in the Welsh Government's Expertise Wales webpages. The university also disseminates information on projects and results in articles on the Advances Wales publication, and as Bangor University is a member of MediWales, can take advantage of this network for further opportunities to disseminate the results.

We will also communicate the key results to participant support groups, so that findings that could benefit participants with sciatica can be disseminated to affected participant groups. In particular we will contact Back Care, the charity for healthier backs, to use their Back Care Journal and Talkback magazine, Pain Concern through their Pain Matters magazine, as well as Arthritis Research UK through its magazine Arthritis Today and online patient materials.

## Intention to publish date

01/01/2019

## Individual participant data (IPD) sharing plan

### IPD sharing plan summary

Stored in repository

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Other publications</a>	lessons learnt from discontinued trial	31/07/2018		Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No