TRIAL 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)

Trial Identification

EudraCT Number –2015-000636-15

ISRCTN –14569274

REC Number –15/WA/0105

Name of **Sponsor:** Bangor University

Funder: NIHR Health Technology Assessment (HTA) project number 12/201/02.

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General Information

This protocol describes the SCIATIC clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial, but centres entering participants for the first time are advised to contact North Wales Organisation for Randomised Trials in Health (NWORTH) in Bangor to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the trial should be referred, in the first instance, to NWORTH.

Compliance

This trial will adhere to the principles of good clinical practice as outlined in the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It will be conducted in compliance with the protocol, the Declaration of Helsinki (South Africa, 1996), the Research Governance Framework for Health and Social Care (Welsh Assembly Government November 2001and Department of Health 2nd July 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

Funding

The SCIATIC trial is being funded by the NIHR Health Technology Assessment (HTA).

Contents

Abbreviations and glossary

AE	Adverse Event
ATLAS	Assessment and Treatment of Leg pain Associated with the Spine
CI	Chief Investigator
CXR	Chest X-Ray
CRF	Case Report Form
DSUR	Development Safety Update Report
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FBC	Full Blood Count
GAC	Global Assessment of Change
GCP	Good Clinical Practice
GP	General Practitioner
DMEC	Data Monitoring Ethics Committee
eGFR	Estimated Glomerular Filtration Rate
HADS	Hospital Anxiety and Depression Scale
Hba1c	Glycosylated Haemoglobin
ICF	Informed Consent Form
ICH	International Committee of Harmonisation
IGRA	Interferon-Gamma Release Assays
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application Service
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LFT	Liver Function Test
MHRA	Medicine and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
NIHR HTA	National Institute for Health Research Health Technology Assessment
NISCHR	*National Institute for Social Care and Health Research*
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NWORTH	North Wales Organisation for Randomised Trials in Health
ODI	Oswestry Disability Index
PSEQ	Pain self-efficacy questionnaire
PI	Principal Investigator

PIC	Patient Identification Centre
PIS	Participant Information Sheet
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
RMDQ	Roland-Morris Disability Questionnaire
RUQ	Resource Use Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Action Plan
SAR	Serious Adverse Reaction
SBI	Sciatica Bothersomeness Index
SBST	STarT Back Screening Tool
SLR	Straight Leg Raise
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMF	Trial Master File
TMG	Trial Management Group
TNF-alpha	Tumour Necrosis Factor
TSC	Trial Steering Committee
U&E	Urea and Electrolytes
WMD	Weighted Mean Difference

1. Background & Rationale

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. It is often associated with numbness or paraesthesia in the same distribution [1]. Sciatica is an important clinical problem for the NHS. Although prevalence rates vary widely between studies, in a trial that used a clinical assessment to establish the presence of sciatica the point prevalence in the general population aged 30-64 years was 4.8% [2]. Some cohort studies have found that most cases resolve spontaneously with 30% having persistent troublesome symptoms at one year, with 20% out of work [3, 4]. However, another cohort found that 55% still had symptoms of sciatica two years later, and 53% after four years (which included 25% who had recovered after two years but had relapsed again by four years) [5].Current care pathways in the NHS typically involve the prescribing of analgesia by their general practitioner, and if troublesome symptoms persist, referral for physiotherapy either in community based physiotherapy services, musculoskeletal interface services or secondary care spinal clinics. If pain persists, patients are referred for more invasive treatment such as epidural corticosteroid injection and eventually disc surgery [6]. However, the evidence for most of these non-surgical treatments is poor [7]; new treatment strategies are needed. At present between 5-15% of patients with sciatica undergo disc surgery [3, 4]. In the NHS in England in 2010/11, 10,203 lumbar discectomies were performed [8]. Based on a Dutch trial which indicated that the cost of sciatica to society represents 13% of all back-pain related costs, the annual impact on the UK economy is £268 million in direct medical costs, and £1.9 billion in indirect costs (inflated from 1998 figures) [9].

Sciatica caused by lumbar nerve root pain usually arises from a prolapsed intervertebral disc [3], not only from compression of the nerve root [10], but also the release of pro-inflammatory factors from the damaged disc [11, 12]. Internal disc rupture that does not result in prolapse can also induce disabling radicular pain [13], and the degree of disc displacement, nerve root enhancement and neural compression on magnetic resonance imaging does not correlate with sciatic symptoms [14]. Corticosteroids have been used in an attempt to reduce the inflammation of the affected nerve root. Intramuscular corticosteroid injections have been tried, but two RCTs comparing them with placebo have found no evidence of efficacy [15]. Injection of corticosteroid into the epidural space should increase the amount of steroid reaching the affected nerve root, and it is a commonly used intervention in the NHS. However, systematic reviews of epidural steroid injections

have reached conflicting views with regard to their efficacy compared with placebo and their effectiveness compared with other treatments [15-18]. They also require to be administered by a specialist, usually as a hospital day case procedure, which increases their cost of administration. Other less invasive treatments to reduce inflammation in the affected nerve root are needed. The most important pro-inflammatory factors released from the prolapsed intervertebral disc is tumour necrosis factor-alpha (TNF-alpha) [11, 12]. The monoclonal antibodies infliximab and adalimumab target TNF-alpha and are increasingly used to control inflammatory disease such as psoriasis, Crohn's disease and rheumatoid arthritis. These so-called 'biological agents' bind specifically to TNF-alpha receptors on the cell surface, and modulate biological responses that are induced or regulated by TNF-alpha, including the inflammatory process [19]. They may also have beneficial effects on the inflamed nerve root in sciatica [20], and have the additional advantage of being administered by intra-venous (infliximab) or subcutaneous (adalimumab) injection in a hospital outpatient clinic, rather than by epidural injection as a hospital day case.

This research is needed now following the recommendations of a recently completed HTA funded systematic review of management strategies for sciatica [21]. In this review the clinical effectiveness of different treatment strategies for sciatica were compared simultaneously using network meta-analysis. Network meta-analysis allows treatment strategies to be ranked in terms of clinical effectiveness with an estimate of the probability that each strategy is best, and provides estimates for all possible pair-wise comparisons, based on both direct and indirect evidence. In terms of overall recovery or global effect biological agents had the highest probability (0.5) of being best and an odds ratio (OR) compared with inactive control of 16, but with very wide 95% credible intervals (95% CrI) of 0.6 to 1,002, reflecting the small number of included studies and lack of data that was available to inform these effect estimates. A credible interval (CrI) is a Bayesian confidence interval. There were large but non-statistically significant effect estimates in favour of biological agents compared with the other treatment strategies including traction (OR 13, 95% CrI 0.4 to 943), exercise therapy (OR 15, 95% CrI 0.4 to 1085), and passive physical therapies (OR 14, 95% CrI 0.5 to 975). In terms of pain intensity, biological agents had the second highest probability of being best (0.2), were found to be statistically significantly better than inactive control but with wide credible intervals, with a weighted mean difference (WMD) of -22 (95% CrI -36 to -8), opioid WMD -31 (95% CrI -53 to -9), or non-opioid analgesia WMD -18 (95% CrI -33 to -2).

Following this HTA review we updated the literature search of biological agents for sciatica. We identified seven RCTs, one non-RCT and one historical cohort trial. We combined the results of six RCTs [22-27] and one non-RCT [28] comparing biological agents with placebo in meta-analyses. We found that biological agents resulted in: better global effects in the short term (around six weeks follow-up) odds ratio (OR) 2.0 (95% CI 0.7 to 6.0), medium term (around six months follow-up) OR 2.7 (95% CI 1.0 to 7.1) and long term (12 months or longer follow-up) OR 2.3 [95% CI 0.5 to 9.7); improved leg pain intensity in the short term weighted mean difference (WMD) -13.6 (95% CI -26.8 to -0.4), medium term WMD -7.0 (95% CI -15.4 to 1.5), but not long term WMD 0.2 (95% CI -20.3 to 20.8); improved Oswestry Disability Index (ODI) in the short term WMD -5.2 (95% CI -14.1 to 3.7), medium term WMD -8.2 (95% CI -14.4 to -2.0), and long term WMD -5.0 (95% CI -11.8 to 1.8). It should be noted that there was heterogeneity in the leg pain intensity and ODI results and improvements were no longer statistically significant when studies were restricted to RCTs. There was a reduction in the need for disc surgery, which was not statistically significant, limited evidence for improved employment outcomes and no difference in the number of adverse effects. There was limited evidence that a biological agent was superior to intra-venous corticosteroids (one historical cohort trial) [29], but not compared with epidural corticosteroid (two RCTs) [27, 30]. We can conclude that there was some evidence of efficacy, but a paucity of evidence for effectiveness for biological agents. Although there was insufficient evidence to change practice, there was sufficient evidence to suggest that a definitive RCT is warranted.

As part of the HTA review of management strategies for sciatica [21] a decision analytic model was developed to estimate the relative cost-effectiveness of these different strategies. Three different treatment pathways were compared. The first pathway was primary care treatments alone (including the categories usual care, activity restriction, advice, non-opioid and opioid analgesia). The second pathway was stepped care starting with primary care treatments and for those who did not improve intermediate care treatment (exercise therapy, passive physical therapy, traction, manipulation, acupuncture and biological agents), epidural steroid injections then finally disc surgery. The third pathway was immediate referral to disc surgery following failed primary care management. The stepped care pathway was the most effective with the most successful treatment strategy being non-opioid analgesia in primary care, followed by biological agents in intermediate care, followed by epidural corticosteroid injection and disc surgery. The place for biological agents in the therapeutic pathway is as a therapeutic option to be used by intermediate care

services in patients who have failed primary care treatment, with the potential to reduce the need for more invasive treatments.

So biological agents have the potential to reduce inflammation and nerve root pain in patients when primary care management has not relieved symptoms, but might they benefit the NHS? Apart from the economic model developed for the HTA review of management strategies for sciatica [21], there have been no economic evaluations of these agents. Although they might be beneficial for patients with sciatica, they are expensive costing £352 for 40mg adalimumab and £420 for 100mg infliximab [31]. Adalimumab is administered by sub-cutaneous injection, but infliximab confers the additional expense of intra-venous injection. We intend to use adalimumab because of its ease of administration, and in order to provide a therapeutic effect lasting one month, two subcutaneous injections can be given two weeks apart. In order to initiate a rapid response we will use the typical starting dosage when treating psoriasis or Crohn's disease of 80mg followed by 40mg [19]. Despite their cost, they may be cost-effective if shown to be sufficiently clinically effective and /or they reduce the need for more expensive treatments such as disc surgery, the average unit cost of which is between £3,676 and £4,971 [31]. The patent for adalimumab is due to expire in 2016, which may result in the development of cheaper biosimilar drugs which can be used in its place. From searches of databases of current trials, we have not identified any large RCTs with a concurrent economic evaluation in a NHS setting.

2. Trial Objectives and Design

2.1 Trial Objectives

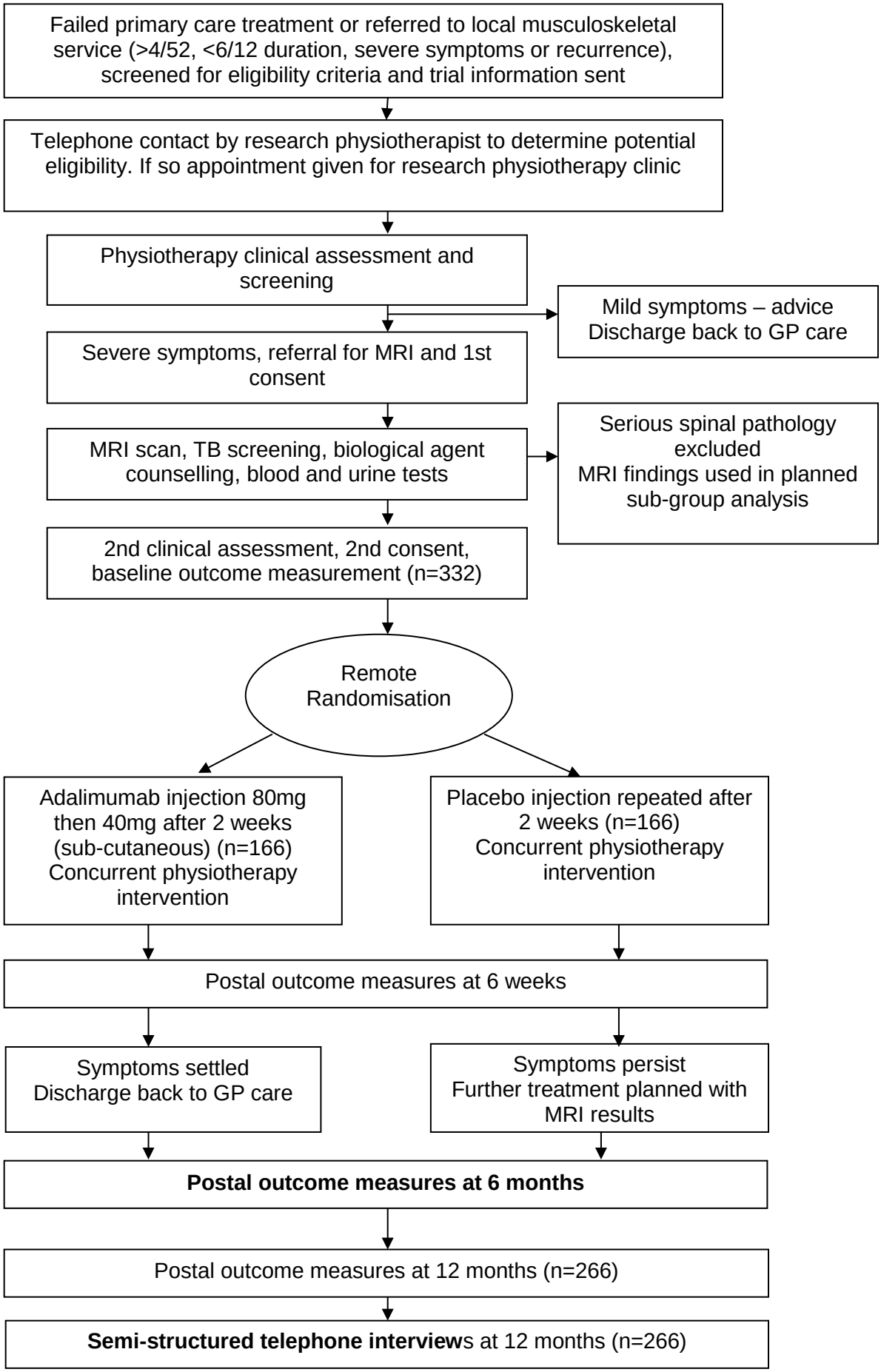
1. To evaluate the effectiveness of subcutaneous injections of adalimumab plus physiotherapy compared with placebo injection of 0.9% sodium chloride plus physiotherapy for patients with sciatica who have failed first line primary care treatment. Potential participants will be identified during primary care consultation, after referral to musculoskeletal service or following a practice database search. The primary effectiveness outcome will be sciatica related health status using the Oswestry Disability Index [32]. 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.

2. 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 [33] at each follow-up visit.

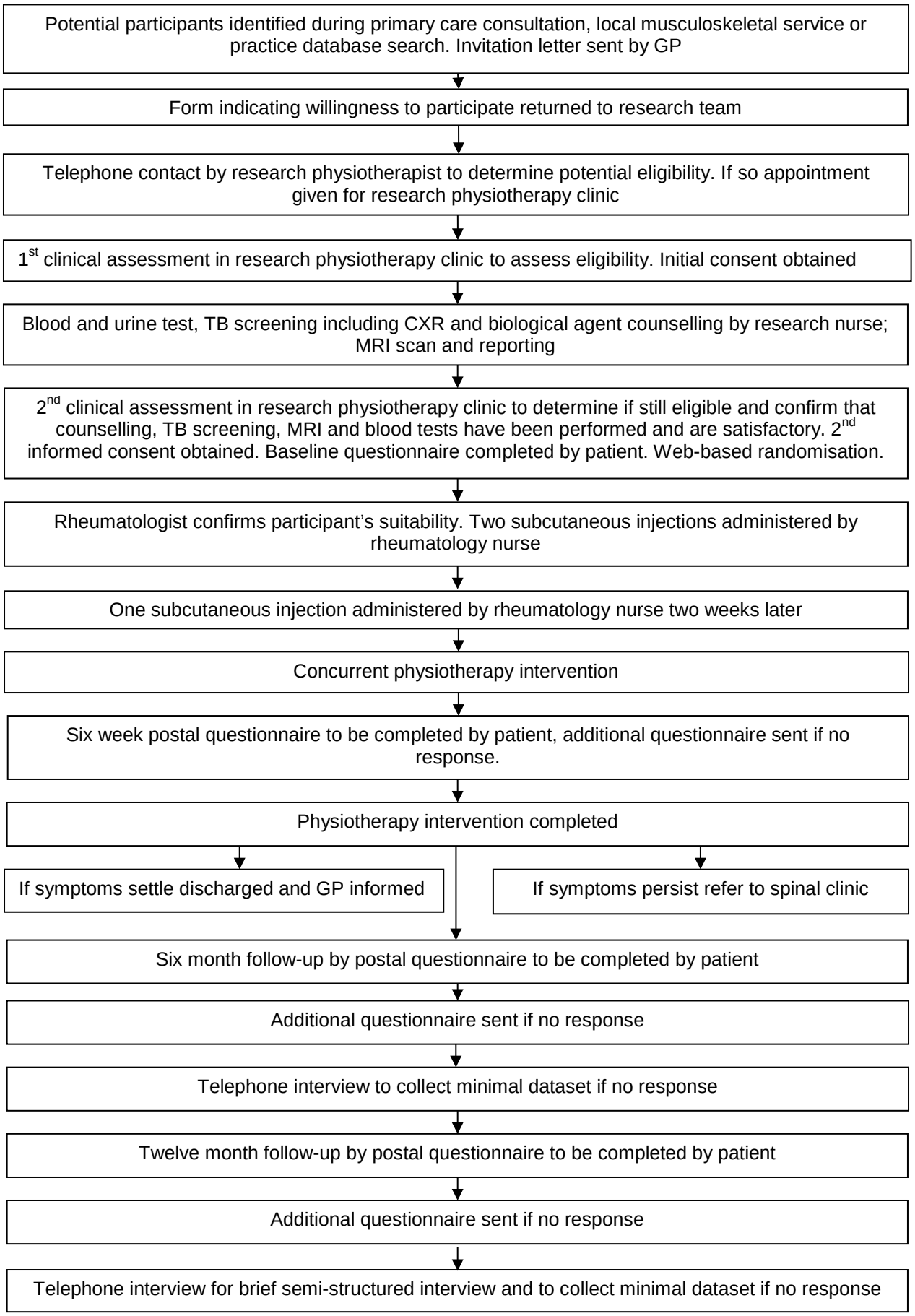
2.2 Trial Design

Multi-centre randomised controlled trial (RCT) of 332 participants recruited from primary care or musculoskeletal services with a concurrent economic evaluation and an internal pilot trial.

2.3 Trial Flowchart



Participant Flowchart



3. Trial Medication

3.1 Investigational Medicinal Product

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells. Its current therapeutic indications are for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis. It is given by sub-cutaneous injection 40mg every other week by sub-cutaneous injection. In Crohn's disease and psoriasis an initial dose of 80mg is given followed by 40mg at week two in order to initiate a more rapid response. A higher dose of 160mg followed by 80mg can be used for a more rapid response, but with a greater risk of adverse effects. Adalimumab's mode of action is that it binds specifically to Tumour Necrosis Factor (TNF-alpha) and neutralizes the biological action of TNF-alpha by blocking its interaction with the p55 and p75 cell surface TNF-alpha receptors. It also modulates biological responses that are induced or regulated by TNF-alpha, including changes in the levels of adhesion molecules responsible for leukocyte migration. Its pharmacokinetic properties were as follows; after subcutaneous injection of a single 40mg dose, absorption and distribution of adalimumab was slow with peak serum concentrations reached about five days after administration. The average absolute bioavailability was 64% and the mean terminal phase half-life was approximately two weeks. Weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The mean steady state trough concentration after 40mg injections every other week was 5µg/ml, and if a loading dose of 80mg was given at week 0 followed by 40mg at week two a trough concentration of 5.5µg/ml was achieved during the induction period.

3.2 Dosing Regimen

In order to achieve a reasonably rapid response without increasing the risk of adverse effects, an initial dose of 80mg given by sub-cutaneous injection will be given followed by an injection of 40mg two weeks later.

3.3 Drug ordering

At each treatment site the local pharmacist on behalf of the principal investigator, or local collaborator, will order the trial medication (adalimumab) and 0.9% Sodium Chloride placebo injections on behalf of the sponsor. The order will request the processing and packaging of a certain number of units and their shipping. It will be in writing (paper or e-mail), and precise enough to avoid any ambiguity. It will be formally authorised and refer to this trial protocol. A qualified pharmacist in each of

the treatment sites, experienced in dealing with trial supplies, will be involved in this process.

3.4 Summary of Product Characteristics

Adalimumab is a licensed drug which will be used off-label for this RCT.
There is no Investigator Brochure therefore the Summary of Product Characteristics produced by the Marketing authorisation holder will be used.

3.5 Blinding operations

It will not be possible to supply indistinguishable ampoules of adalimumab and 0.9% Sodium Chloride placebo because the adalimumab is only available in its own unique injection device. It will not be possible to blind the pharmacy or the person administering the injection. Trial specific procedures will document the measures that will be in place to blind the trial participant receiving the injection and all other clinicians in the trial; all relevant trial staff will be trained in these procedures at the individual site initiation. Participant's medical notes will be marked to show they are participating in the SCIATiC trial which is a blinded trial. This blinding will be maintained until all data entry and processing are complete and the database has been locked. In an emergency situation an on-call pharmacist will be available at all times so that the identification of the product can be revealed with the permission of the Chief Investigator or Principal Investigator at each site.
Each participant's prescription will indicate his or her unique identifier number, injection for the sciatic trial but will not specify active or placebo. A telephone number will also be available within pharmacy so that the code can be broken in an emergency.

3.6 Packaging

The adalimumab injection must not be exposed to light prior to use, so will be kept in its original packaging. The adalimumab and 0.9% Sodium Chloride injections will be placed in identical secondary packaging with appropriate labelling.
The secondary packaging containing the adalimumab or placebo 0.9% Sodium Chloride injections will be labelled appropriately and comply with the requirements of Directive 91/356 as amended for IMPs [34].

3.7 Labelling

The labelling will ensure that trial participants are protected, for example there will be clear instructions on how to use and store the product. The following information will be included on labels:

- Name, address and telephone number of the sponsor Bangor University,
- Pharmaceutical dosage and form, route of administration, quantity of dosage units,
- Batch and/or serial number;
- Trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
- Trial participant identification number and the visit number;
- Directions for use;
- The following phrase “For clinical trial use only”;
- Storage conditions;
- Period of use (use-by date, expiry date as applicable), in month/year format.

The labelling will not make any reference to group allocation. The address and telephone number of the main contact for information on the product, clinical trial and for emergency un-blinding will not appear on the label as the participant will be given a leaflet or card which provides these details and who the local contact is, in the case of any adverse events during the trial and they will be instructed to keep this in their possession at all times.

3.8 Release of Batches

The adalimumab and 0.9% Sodium Chloride injections will be ordered by the pharmacy in each treatment site using their usual supplier. A copy of the order will be retained in the Investigator site file. Shipping of the adalimumab and placebo 0.9% Sodium Chloride injections will be conducted according to the suppliers’ usual best practice. A detailed record of the shipments from the supplier will be maintained, which will mention to whom the shipment is addressed and delivered.

3.9 Storage and pharmacy controls

The Pharmacies in each of the treatment sites will have facilities that allow for the adalimumab and placebo steroid injections that will be used in the trial to be stored separately from normal pharmacy stock in an area with restricted access. The adalimumab will be stored in its original packaging in refrigerators kept at between 2 and 8 degrees Celsius. Arrangements are in place to monitor the temperature of the

storage refrigerators. 0.9% Sodium Chloride will be stored as per pharmacy procedures, avoiding excessive heat. It is recommended the product be stored at room temp. (25°C) brief exposure up to 40°C does not adversely affect the product.

3.10 Prescriptions for IMPs

The IMPs will be prescribed on a trial-specific clinical trial prescription form by a rheumatologist who is recognised as participating in the trial and has signed the delegation and signature log. Participant's suitability will be confirmed via the CRF which will be completed after all screening tests are performed. Prescriptions for IMPs will clearly identify the clinical trial, the participant's unique randomisation number, and trial medication required.

3.11 Recall of drug supplies

Procedures for retrieving IMPs and documenting this retrieval will be agreed by the Sponsor or their delegate in collaboration with the manufacturer and participating site pharmacy procedures. The pharmacist on each site will keep accountability logs (which will be provided by the sponsor or their delegate), of all injections used during the trial (batch numbers and use by dates). The procurement pharmacist will receive a notification of re-call from the MHRA and will disseminate to all pharmacists. This is general to all registered pharmacists. The sponsor or their delegate will ensure that adequate controls (e.g. drug accountability logs) are in place to enable accurate stock reconciliation. The IMP recall reconciliation form will be used to record the recall of IMP from trial sites. Returned IMPs will be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned IMPs will be kept. The sponsor or their delegate will be responsible for the destruction of unused or returned IMPs. IMPs will not be destroyed without prior written authorisation by the sponsor or their delegate. The delivered, used and recovered quantities of product will be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused IMPs will be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations will be carried out in such a manner that all operations will be accounted for. The records will be kept by the sponsor or delegated person. When destruction of IMPs takes place a dated certificate of, or receipt for destruction will be provided by the sponsor or their delegate. These documents will clearly identify, or allow traceability to, the batches or participant

identification numbers involved and the actual quantities destroyed, in the form of a drug accountability log.

3.12 Drug Accountability Logs

As per sponsor requirements, drug accountability logs will be used to record deliveries from the treatment sites, drugs dispensed to participants, unused drugs, returns and disposal records. The drug accountability logs will be provided by the sponsor or their delegate The records will also include dates for deliveries, drugs dispensed and returned; batch numbers; expiry dates, drug serial number (unique codes) and participant ID numbers. Periodic stock checks will be performed. If a database is used for stock allocation, then the physical count at the trial site(s) should be cross checked against the database as well. Any anomalies must be reported to the trial manager and investigated. For information of monitoring please refer to the NWORTH Monitoring SOP 3.07.

3.13 Incident reporting

Any incidents relating to discrepancies with the IMP (e.g. labelling anomalies, storage issues such as temperature excursion, errors noted from stock checks) will be reported to the NWORTH trial manager immediately so that they can be promptly and thoroughly investigated.

4. Selection and Withdrawal of Subjects

The RCT will recruit from sites overseen by five collaborating centres (North Wales; London; Keele; Nottingham; Cardiff). Each collaborating centre will oversee one or more treatment sites which will be delegated responsibility for delivering the interventions. Each collaborating centre will oversee a number of patient identification centres (PICs) which will consist of general medical practices and local musculoskeletal services. The collaborating centres, treatment sites and the PICs will sign an agreement with Bangor University (the trial Sponsor) that details what is expected from them. NWORTH will ensure that all regulatory approvals are in place and will provide each site with an Investigator Site File (ISF). The following documentation must be completed and received by NWORTH in order for a site to begin recruitment:

Local research and development approval, delegation log i.e. a full list of research staff involved in the trial and their responsibilities, CVs, copy of their GCP certificate and signed Site Specific Information (SSI) form.

All documentation must be stored in the Investigator Site File (ISF) at the site and PIC and in the Trial Master File (TMF) at NWORTH. NWORTH must be notified of any changes to the trial personnel and their responsibilities during the running of the trial and the respective trial files must contain this up-to-date information.

When giving informed consent to participate in the RCT, participants are consenting to be randomised and to engage in follow up data collection. If the participant explicitly states their wish not to contribute further data to the trial, NWORTH should be informed. A completed withdrawal CRF should be scanned and emailed to NWORTH by the collaborating centre with the hard copy to follow soon after. Participants do not have to give a reason for their withdrawal but centres and sites should make a reasonable attempt to find out why.

4.1 Target population

The target population are adults with suspected sciatica who have failed primary care treatment. This will be defined as troublesome symptoms (e.g. back and leg pain, pins and needles, numbness in leg, weakness), persisting for longer than four weeks, and less than six months. As we envisage that the recruitment process outlined below will take at least four weeks before participants are randomised we will not have a lower time limit for duration of symptoms for identifying the target population and will have an upper time limit of twenty weeks. These patients will be identified in three ways:

- By their GP
- Following a search of the general practice patient record database
- After referral to local musculoskeletal services

4.1.1 GP referral

Patients identified during the primary care consultation with suspected sciatica will be provided with information about the trial and invited if interested to return the reply slip to the research team in the pre-paid envelope. In some centres the primary care database will display “pop up” screen messages to remind general practitioners about the study when potential patients consult.

4.1.2 Following a search of general practice patient record database

Potential participants will be identified by regular searches of the general practice patient’s record database by the practice management staff directed by research

officers from either the NISCHR workforce in Wales or the local Clinical Research Network in England. The database will be searched for diagnostic codes for sciatica. Participants will be excluded if they have known serious spinal pathology or contra-indication to adalimumab injection, such as serious infection (e.g. active or latent tuberculosis), transplanted organ, demyelinating disorders, malignancy, cardiac failure, low white count, or pregnancy. Those identified as potentially eligible will be invited to participate by a written invitation which will include key screening questions from their GP on the practice's headed notepaper and hand signed by a GP. Those who are interested will return the reply slip to the research team in the pre-paid envelope.

4.1.3 Local musculoskeletal services

Potential participants with suspected sciatica will also be identified from referrals to local musculoskeletal services. Those identified will be invited to participate by a written invitation which will include key screening questions from the local service on headed notepaper. Those who are interested will return the reply slip to the research team in the pre-paid envelope.

4.1.4 Telephone contact by the Research Physiotherapist

All those who have contacted the research team to state they are interested in participating will be sent a participant information sheet and will be contacted by telephone by the research physiotherapist. The telephone call will determine whether they have unilateral leg pain and if back pain is present, that leg pain intensity is worse than, or as bad as, the back pain. It will also determine whether symptoms have persisted for longer than 20 weeks (to allow participants to be within the six months limit at randomisation). Finally, the telephone call will allow them to discuss any questions that they may have about the study or their symptoms.

4.1.5 First clinical assessment in research physiotherapy clinic

Those that satisfy the eligibility criteria will be given an appointment slot in a research clinic run by research physiotherapists. At this research clinic all potential participants will be assessed by the research physiotherapist for eligibility. Eligible participants who give initial consent will be registered and provided with a unique participant registration number. The following data will be recorded on case report forms:

- Demographic details such as age, gender, height and weight;
- Clinical findings such as pain location, pain duration, other presenting complaints, straight leg raise test (left and right), femoral stretch test, muscle

power, pin prick and light touch sensation, quadriceps and Achilles tendon reflexes.

The research physiotherapist will arrange for the participant to have the following blood tests taken by the phlebotomist to exclude haematological, and biochemical abnormalities: FBC, U+E, eGFR, LFT and HbA1c. The participant will receive tuberculosis (TB) screening according to local practice (section 4.6), and biological agents counselling, the research physiotherapist will then arrange an appointment for magnetic resonance imaging (MRI) to exclude serious spinal pathology. All of these tests will be completed within 2-3 weeks of their initial clinic visit and will be recorded on the case report forms. The presence or absence of a disc prolapse on the MRI will not be used as an inclusion criterion, because the degree of disc displacement, nerve root enhancement or neural compression found on MRI does not correlate with sciatic symptoms [14]. The MRI will be reported by the local radiologist using a trial specific standard operating procedure (SOP). The initial report will state whether or not the participant has serious spinal pathology that requires a different treatment. A full MRI report will only be available after completion of the study. Individual results will be made available if a report is needed in an emergency, or if a spinal surgery referral is being contemplated.

The research physiotherapist will ensure that the participant has had all the required tests, if there is any issue that requires action then the participants referring GP or musculoskeletal clinician will be informed. When MRI has excluded serious spinal pathology participants will be contacted by the research physiotherapists either by telephone or post to attend the research clinic, where they will receive a second clinical assessment by the research physiotherapist, which will be 2-3 weeks after their initial visit to assess if they are still eligible. If they are still eligible further consent will be obtained for trial entry and randomisation where they will be provided with a unique participant randomisation number.

4.2 Inclusion criteria

- 18 years of age and older;
- Clinical features of sciatica
- Leg pain worse or as bad as back pain, obtained by asking the participant
- 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
- And one of the following:-

- Positive neural tension test such as Straight leg raise test (SLR) restricted <50 degrees by leg pain; positive femoral stretch test
- Muscle weakness or loss of tendon reflex affecting one myotome
- Loss of sensation in a dermatomal distribution

- Persistent symptoms for at least 4 weeks and less than six months despite first line treatment in primary care; obtained by asking the participant
- Moderate to high severity (≥30) on Oswestry Disability Index [32].
- Female partners of sexually active male participants should use adequate contraceptives for at least five months after the last injection. Female participants should have a negative urine pregnancy test within two weeks prior to randomisation, unless they are post-menopausal or have had a sterilisation operation. Sexually active men of female participants must also use adequate contraceptive methods. The researcher will ensure that the risks and consequences of not using adequate contraceptives are fully understood by the participants and will provide information and pathways as deemed necessary.

4.3 Exclusion criteria

- Symptoms persisting for longer than six months (obtained by asking the participant)
- A previous episode of sciatica in the last six months
- 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
- 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)
- Incidental serious pathology identified by MRI (e.g. adrenal tumour)
- Neurological deficit involving muscle weakness requiring an urgent spinal surgery assessment e.g. foot drop
- Widespread pain throughout the body including the upper limb [35] (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).

- Prior use of biological agents targeting TNF-alpha within the previous six months obtained from the medical records and by asking participant;
- Previous lumbar spinal surgery obtained from the medical records and by asking the participant;
- 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;
- Pregnant or breast-feeding (women must not breastfeed for at least five months after the last adalimumab injection).
- Unable to communicate in English or Welsh.
- Unable or unwilling to give informed consent.

4.4 Informed consent

At the initial physiotherapy clinic the research physiotherapist will determine preliminary eligibility and the nature of the trial will be explained and a repeat participant information sheet (PIS) given. The PIS will have been approved by the ethics committee and will set out all key information including: the practicalities of the trial, the possible benefits, risks, and trial assessments. Participants will be registered onto the trial and details will be recorded on a database and a screening log at each of the trial treatment sites and participants will be assigned a unique participant registration identification number. Anonymised details labelled with the unique participant registration identification number will be transferred to a separate database in NWORTH, which will be used for recording all of the trial data. This will ensure that outcome measurement and statistical analysis will be performed blind to treatment allocation. All databases will be password protected. The participant consent forms will be stored in a locked filing cabinet in each treatment site. Clinical findings will be recorded on case report forms.

Eligible participants who give initial consent will have blood tests to exclude haematological and biochemical abnormalities (FBC, U+E, eGFR, LFT, Hba1c). They

will receive tuberculosis (TB) screening including a plain chest radiograph, biological agents counselling and magnetic resonance imaging (MRI) to exclude serious spinal pathology within 2-3 weeks of their initial visit. When MRI has excluded serious spinal pathology, TB screening, pregnancy test for eligible women and biological agent counselling has been completed, participants will attend a further appointment with the research physiotherapist. A second clinical assessment will be performed and if they are still eligible a second informed consent form, approved by the ethics committee will be completed in order to enter the RCT, the participant will be randomised by the research physiotherapist using a remote web-based system (See section 4.9). A letter will be sent to the participant's GP by the treatment site to inform them that the participant is taking part in the trial and request that the GP make a note of this in the patient record. In addition GPs will be requested to inform the trial team if they become aware the participant has experienced an adverse event or serious adverse event during the trial. (See section 7.0).

Three copies of the consent form will be signed by the participant. The original will be kept by the research team, one copy will be kept by the participant and the third will be filed in the participants' hospital medical records. All participant information sheets, letters of invitation, consent forms will be provided in Welsh and English in the two Welsh centres.

4.5 Magnetic Resonance Imaging

Participants who have given initial informed consent will receive magnetic resonance imaging (MRI) to exclude serious spinal pathology, but the presence or absence of a disc prolapse will not be used as an inclusion criterion. The MRI scans will be read and reported by a local radiologist using a trial SOP at each treatment site, who is independent of the trial team and only results which show serious pathology or suspected serious pathology will be revealed to the research team, referring GP and the musculoskeletal clinician who will exclude the participant and refer for urgent assessment. Otherwise the research team will be informed that no serious spinal pathology was identified. The findings of the MRI will only be available to the participants treating clinician after completion of the study. Individual results will be made available if a report is needed in an emergency, or if a spinal surgery or epidural injection referral is being contemplated and will be shared with the clinical team, referring GP and the musculoskeletal clinician The MRI findings will also be used in a planned *a priori* sub-group analysis. For clinical purposes each site will provide a clinical report of the MRI from radiologists in each site. For the purpose of reporting standardised findings for research radiologists from Betsi Cadwaladr

University Health Board (BCUHB) (MG) and Keele University will report all of the MRI for all trial participants. The radiologist will interpret the report according to the MRI findings only.

4.6 Tuberculosis screening and biological agent counselling

Centres	T-SPOT	Chest X-Ray	IGRA
London		X	X
Keele	X	X	
Nottingham	X	X	
Cardiff	X	X	
North Wales	X	X	

The screening and counselling protocols used routinely by the rheumatology departments in each of the treatment sites will be used and administered by an experienced rheumatology specialist nurse. All of the participating centres have access to either a specialist tuberculosis clinic, or an infectious disease service, where any identified cases will be referred and managed.

4.7 Second clinical assessment in research physiotherapy clinic

Participants will attend a second appointment with the research physiotherapist 2-3 weeks after the initial appointment, after the MRI has been reported and following TB screening and biological agent counselling. A second clinical assessment will be performed and all the results of the tests performed will be checked, if the participant remains eligible a second consent form will be completed. The participant will complete a baseline questionnaire and they will be randomised using a remote web-based system. If they no longer fulfil the criteria for trial entry, because their symptoms have improved at or below the 30 point threshold on the ODI, they will be given advice about managing their remaining symptoms and will be discharged back to the care of their general practitioner. Clinical findings will be recorded on case report forms.

4.8 Registration

Procedures set out in the NWORTH trials unit's SOP's will be followed. Once the first consent has been obtained participants' details will be recorded on a database in the trial centres and assigned a unique participant identification number. Anonymised

details labelled with the unique participant identification number will be transferred to a separate database in NWORTH which will be used for recording all of the trial data. All databases will be password protected. The participant consent forms will be stored in a locked filing cabinet in each treatment site. The participant's GP will be informed in writing about their participation in the trial.

4.9 Randomisation

After completion of the second consent form and baseline outcome measures have been collected, participants will be individually randomised. Randomisation to SCIATiC trial will be achieved by secure web access to the remote randomisation system at NWORTH at Bangor University. This system will be maintained and monitored independently of the trial statistician and any trial staff who need to remain blind to the treatment allocation. In order to protect against subversion while ensuring that the trial maintains good balance to the allocation ratio of 1.1, both within each stratification variable and across the trial, the randomisation will be performed using a dynamic adaptive randomisation algorithm [36] Participants will be stratified by: (1) treatment centre and (2) presence of neurological signs (motor weakness or sensory loss). The research physiotherapist who obtained informed consent will request the randomisation code from the web-based randomisation system the result of which will be e-mailed to the pharmacy and the rheumatology nurse, but not the research physiotherapist. The dispensing pharmacist will log and dispense the appropriate injection in line with MHRA guidelines. The injection should be given on the day of randomisation, however, if this is not possible a further appointment will be arranged by the research physiotherapist so that the treatment can be given within three days from randomisation.

4.10 Withdrawal of participants

Participant withdrawal from the trial will not affect their medical care, which will be emphasised in the participant information sheet. Non-completion of any one follow-up will not constitute formal withdrawal from the trial, and unless the participant requests withdrawal of their data completely, may be used to impute values for the analysis. The imputation of missing values will ensure that the dataset is utilised to its full power. The full imputation details will be pre-specified as part of the statistical analysis plan.

4.11 Expected Duration of Trial

We will recruit participants over a twenty month period and follow them up for twelve months.

5. Trial Procedures

5.1 Sub-cutaneous injections

All participants will be randomised to receive two doses of subcutaneous injection two weeks apart at the level of the lumbar paravertebral muscles. The intervention group will receive 80mg adalimumab followed by 40mg [19] 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 as the intervention group.

5.1.1 Injection Process

The injections will be prescribed by a consultant rheumatologist and administered by a rheumatology nurse experienced in the administration of these injections. The first injection should be given on the same day as randomisation however, if this is not possible a further appointment will be arranged by the research physiotherapist so that the treatment can be given within three days from randomisation. It will not be possible to make the adalimumab and placebo syringes indistinguishable in appearance nor will it be possible to blind the pharmacy or the rheumatology nurse who administers the injections. Blinding for the participants and the other clinicians will be maintained using the following strategies:-. The rheumatologist will write a prescription for 'SCIATiC trial injection' and will be kept blind to treatment allocation. The research physiotherapist who obtained informed consent will request the randomisation code from a web-based randomisation system. The randomisation code will not be sent to this physiotherapist but will be e-mailed to the pharmacy and the rheumatology nurse. The rheumatology nurse, will collect the injection from pharmacy which will be carried from pharmacy in an undistinguishable box containing the adalimumab inside its original packaging or the 0.9% sodium chloride ampoules. Communication between participant and research nurse concerning the injection will be kept to a minimum, and the research nurse will administer the subcutaneous injections into the participant's posterior thigh muscles. The research physiotherapist will not be present and will not communicate with the research nurse about the injection. In addition, in order to provide reassurance that other clinicians will not be present, a log will be kept of all people present in the room when each injection is

administered. All research staff will receive full training on the blinding procedures. In order to assess whether blinding has been maintained the participants will be asked to complete a five point Likert scale that asks whether the participant considers treatments to be:

1. Definitely in the 0.9% sodium chloride injection group
2. More likely to be in the 0.9% sodium chloride injection group
3. Equally likely to be in the 0.9% sodium chloride injection group or the adalimumab injection group
4. More likely to be in the adalimumab injection group
5. Definitely in the adalimumab injection group

5.2 Concurrent physiotherapy

Physiotherapy is usually considered normal practice for those participants that fail to improve with GP care alone. In this trial we are investigating the effectiveness of adalimumab in addition to physiotherapy. Current evidence on physiotherapy interventions for participants with sciatica indicates that specific exercise approaches (directional-preference based exercises or 'McKenzie' exercises based on certain spinal movements with or without manual therapy techniques) seem to improve pain for these participants [38]. There is also evidence that physiotherapy treatments (in the form of exercises) added to GP care, benefits participants experiencing severe levels of pain and disability due to their sciatica symptoms [39]. Regimes including strengthening exercises of the lumbar and pelvic muscles also show some promise in terms of improvements in this group of participants [40]. 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 by 'treating' physiotherapists, and not by the 'research' physiotherapists who are carrying out the assessments of eligibility, and randomisation. The physiotherapy intervention will consist of a package of directional preference (McKenzie), strengthening exercises or other, appropriate for the individual patient, exercises [38, 39] and manipulative techniques that have been determined by consensus using a panel of extended scope physiotherapists. Treatment will take into account and address participants' individual needs including clinical monitoring, appropriate advice and reassurance, assessment of psychosocial obstacles to recovery, such as excessive worrying or unhelpful beliefs about physical activity, encouragement of appropriate, gradual return to full function including work where applicable. The first session will last approximately 45 minutes with subsequent sessions lasting 30

minutes each. The therapy sessions will be provided over a period of 12 weeks. The number of sessions provided will be determined by participant and therapist preference and also response to treatment. We will capture and describe these aspects of physiotherapy treatment as part of the trial. In our proposed pathway the physiotherapy treatment starts at the same time as the injection intervention in both arms of the trial. Participants will be discouraged from receiving any other NHS-based co-intervention until this physiotherapy treatment has finished.

5.3 Clinical management of persistent symptoms

Once the participants have completed their course of physiotherapy, if their symptoms have settled or are improving, no further intervention will be organised. They will be discharged to the care of their general practitioner and followed up by the research team as described in this protocol. If troublesome symptoms persist then further treatment will be planned as appropriate by referral to musculoskeletal interface clinics or secondary care specialists according to local arrangement in each of the centres. Further treatment will be at the discretion of the treating clinicians and may include epidural corticosteroid injections or referral for disc surgery. The full result of the MRI scan will be made available if a spinal surgery referral is being contemplated. All additional treatments will be recorded in detail in a case report form (CRF).

5.4 Internal pilot trial

The pilot will build on previous research in this participant group undertaken by team members [6, 30, 41], which has already provided information on trial administration, the characteristics of sciatica participants and the effects of biological treatments from previous studies [42]. The internal pilot will rehearse the procedures and logistics to be undertaken in the main trial. It will assess the feasibility of the arrangements for delivering the interventions, recruitment rate and initial retention rate. The internal pilot will be based on the first 50 participants recruited into the trial. We plan to start recruitment in two centres (including North Wales and London) and then to roll out recruitment in the other three centres over the next three months. We expect the recruitment rate to build over the first three months up to the target rate of four participants per collaborating centre per month. We anticipate that this will take seven months. The indicative stopping criteria at the end of this internal pilot will be recruitment which fails to reach 80% of the planned recruitment rate target, drop outs up until the six week postal questionnaire assessment exceeding 20%, or more than one centre failing to commence recruiting. Mindful of the problem of inappropriate

stopping of a trial if the reasons for the delay are identified and solved the Data Management and Ethical Committee (DMEC) will then make recommendations to the Trial Steering Committee (TSC), and the HTA manager for discussion and decision on stopping the trial. Any procedural changes identified in the pilot would be implemented across all trial sites subject to ethical approval of the appropriate major amendment. Data from participants in the internal pilot will be automatically rolled into the main trial data unless the trial management group believe that data to be incompatible with the remaining data [40]. No interim analysis at the primary endpoint (one year) is proposed and therefore this internal pilot will not affect the overall power of the trial. Wittes and Brittain's [42] method will be used for sample size re-calculation if required. More details in how to implement this will be pre-specified in the statistical analysis plan (SAP), which will be approved by the TSC before the start of any data analysis.

Data collection

	STUDY PERIOD				Follow up period		
	Enrolment	**Randomisation (within 2-3 weeks of registration)**	**Treatment Visit 1 (within 3 days of randomisation)**	**Treatment Visit 2**	**6 week**	**6 month**	**12 month**
Time point:							
Eligibility	X	X					
Informed Consent	X	X					
Registration to Trial	X						
FBC	X						
Urine pregnancy test	X						
U&E's	X						
TB Screening	X						
MRI	X						
MRI reporting*	X*						X*
Eligibility confirmed	X	X					
Randomisation		X					
Subcutaneous Injection of allocated treatment			X	X			
Physiotherapy Treatment				X	X		
ODI		X			X	X	X
EQ-5D-5L		X			X	X	X
RMDQ		X			X	X	X
SBI		X			X	X	X
STarT Back Tool		X					
PSEQ		X			X	X	X
HADS		X			X	X	X
TSK		X			X	X	X
RUQ		X			X	X	X
Pain Outcome		X			X	X	X
Manikin pain diagram		X			X	X	X
Pain Duration		X					
Pain Trajectory		X					
Days of work		X			X	X	X
Global Assessment of change					X	X	X
Adverse Events		X	X	X	X	X	

*The findings of the MRI will only be available to the participants treating clinician after completion of the study. Individual results will be made available if a report is needed in an emergency, or if a spinal surgery referral is being contemplated and will be shared with the clinical team, referring GP and the musculoskeletal clinician

6. Primary outcome

The primary clinical outcome will be back pain specific disability measured using the Oswestry Disability Index [32] 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.

6.1 Outcome measures

6.1.1 Condition specific outcomes

- Back pain specific disability using the Oswestry Disability Index [32]

The Oswestry Disability Index is an outcome assessment tool that is used to measure a participant's impairment and quality of life (i.e., how badly the pain has affected their life). The participant questionnaire contains topics concerning intensity of pain, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each topic category is followed by six statements describing different potential scenarios in the participant's life relating to the topic. The participant then checks the statement which most closely resembles their situation. Each question is scored on a scale of 0-5 with the first statement being zero and indicating the least amount of disability and the last statement is scored 5 indicating most severe disability. The index is scored from 0 to 100. Zero is equated with no disability and 100 being maximum disability. It will be used at the first clinical assessment to assess eligibility and also at the second clinical assessment to confirm eligibility. If recruited onto the trial this will be used as the baseline measurement. It will also be measured at follow-up after six weeks, six and twelve months.

- Leg pain related functional disability using the leg pain version of the Roland–Morris Disability Questionnaire [43, 44]

The Roland-Morris Disability Questionnaire (RMDQ) is a measure of disability where greater levels of disability are reflected by higher numbers on a 24-point scale.
The RMDQ is a self-administered outcome measure. Participants are asked to read the list of 24 sentences and placing a tick against appropriate questions based on how they feel each sentence describes them today. If the sentence does not describe their symptoms today, participants are asked to leave the space next to the sentence blank. Participants are asked to tick next to the sentence if they are sure it describes them today. The RMDQ is scored by adding up the number of items checked by the participant. The score can therefore vary from 0 to 24. If participant indicate in any way that an item is not applicable to them, the item is scored 'No', i.e. the

denominator remains 24.It will be measured at baseline, six weeks, six and twelve months follow-up.

- Leg pain interference using the Sciatica Bothersomeness Index (SBI) [45].

This is an index based on participants reporting of symptoms which reflects the trouble the participant is going through with his/her sciatica symptoms. The index includes self-reported ratings of symptom intensity of: leg pain; numbness or tingling in the leg, foot or groin; weakness in the leg/foot; back or leg pain while sitting. Each symptom item is rated on a scale from 0 to 6, with 0 being not bothersome, 3 somewhat bothersome and 6 extremely bothersome. It will be measured at baseline, six weeks, six and twelve months follow-up.

- Pain location using a pain manikin [46]. This is a picture of a human figure (manikin) on which pain is indicated by the participant and can be used to measure musculoskeletal pain.

It will be measured at baseline, six weeks, six and twelve months follow-up.

6.1.2 Generic outcomes

- Health utility using EQ-5D-5L [33].

This is a participant completed index of health related quality of life, which gives a weight to different health states. It consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each has five levels of severity (no problems/some /moderate problems / extreme problems and unable to). It will be used at baseline, six weeks, six and twelve months follow-up. It allows the calculation of quality adjusted life years (QALYs), using area under the curve method which will be used as part of the economic analysis.

- Global assessment of change since baseline

The global assessment of change is a measure of changes in levels of pain over a set time period. It will be measured at six weeks, six and twelve months follow-up.

6.1.3 Psychological outcomes

- Anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) [47].

This is a participant completed outcome measure of anxiety and depression. It is designed to measure anxiety and depression in participants with physical health problems. It has seven items related to common symptoms of anxiety and 7 for depression. Participants are asked whether they experience the symptom definitely,

sometimes, not much or not at all. The HADS was designed for use in the hospital setting but has been used successfully with the general population. It will be used at baseline, six weeks, six and twelve months follow-up.

6.1.4 Use of health care and social care services

- Resource Use Questionnaire (RUQ) [48, 49].

This is used for collecting retrospective information about trial participants' use of health and social care services, out of pocket expenses and lost earnings. It will be administered at baseline, six weeks, six and twelve months follow-up.

6.1.5 Employment

- Questions on employment status, work absence, sick certification and self-certification.

These will be used at baseline, six weeks, six and twelve months follow-up.

6.1.6 Process Measures (potential predictors and mediators of outcome)

Risk of poor outcome using the

- STarT back screening tool [50].

This screening tool assesses patients' risk of persistent disabling pain. Patients risk subgroup (low, medium or high risk) has been shown by team members to be predictive of outcomes, including patients with back pain and with suspected sciatica. This will be measured at baseline only.

- Pain trajectory based on a single question [51].

This question is used to classify low back pain duration and asks "How long is it since you had a whole month without any back pain?" There are seven discrete response categories:- Less than three months, three to six months, seven to twelve months, one to two years, three to five years, six to ten years and more than ten years. This shows that recalled duration of pain is a predictor of outcome in low back pain patients, independent of baseline severity and psychological status.

- Pain self-efficacy questionnaire (PSEQ) [52].

The PSEQ is a 10-item questionnaire, developed to assess the confidence people with ongoing pain have in performing activities while in pain. The PSEQ is applicable to all persisting pain presentation. It covers a range of functions, including household chores, socialising, work, as well as coping with pain without medication. It will be used at baseline, six weeks, six and twelve months follow-up.

- Fear avoidance beliefs using the Tampa Scale of Kinesiophobia [53]

The TSK is a 17-item checklist that is used to measure the fear of movement (re)injury related to chronic back pain. The scale is based on the model of fear avoidance, fear of work related activities, and fear of movement/re-injury. It will be used at baseline, six weeks, six and twelve months follow-up.

6.2 Follow up

The questionnaires will follow best practice in their design to maximise response rate, participants will receive alerts prior to questionnaires being sent out and regular newsletters notifying participants when questionnaires have been sent. Non-responders to the postal questionnaires will be sent a postcard reminder, an additional copy of the questionnaire, and if there is still not response we will attempt to collect a minimum dataset over the telephone. The baseline questionnaire will be administered by the research physiotherapists, and completed by the participant. We will send follow-up postal questionnaires at six weeks, six and twelve months. Non-responders will be sent a reminder postcard and then an additional copy of the questionnaire. Persistent non-responders will be contacted by telephone in order to collect a minimum dataset. Two weeks after the twelve month questionnaire is sent, all participants will be contacted by telephone. As well as collecting a minimum dataset from non-responders, it will allow a brief semi-structured interview asking all participants about their overall experience of the trial and subsequent follow-up treatment. Blinding to treatment allocation will be maintained during these telephone interviews. Once again, in order to assess whether blinding has been maintained participants will also be asked to complete a five point Likert scale concerning which treatment group they believed that they were in.

7. Assessment of Safety

The procedures regarding safety monitoring, pharmacovigilance and urgent safety measures will be as described in NWORTH SOPs 4.03 and 4.06. As part of site initiation, training will include an overview of possible side effects/potential adverse reactions associated with adalimumab.

7.1 Recording Adverse Events and Adverse Reactions

All trial staff and clinicians in contact with trial participants will be responsible for noting adverse events that are reported by the participant and making them known to appropriate medical staff. Trial participants will be encouraged from the outset of the trial to contact the research team at the time of an event occurring. Participants will

be given a leaflet or card containing a contact address and telephone number which they will be encouraged to contact should they experience any adverse event. All adverse events including non-serious adverse events will be recorded in the participant's medical records and the participant's Case Report Form. All adverse events as defined should be reported up to 1 month from the conclusion of all physiotherapy defined intervention. Adverse events will include:

- An exacerbation of a pre-existing illness.
- An increase in frequency or intensity of a pre-existing episodic condition.
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration.
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the trial treatment.

The following will not be included as adverse events:

- Medical or surgical procedures -where the condition which leads to the procedure is the adverse event.
- Pre-existing disease or conditions present before treatment that do not worsen.
- Overdose of medication without signs or symptoms.

Known adverse reactions to adalimumab recorded in the SMPC include:

Blood and lymphatic system disorders	
Leucopoenia (including neutropenia and agranulocytosis)	Very common
Anaemia	Very common
Leucocytosis	Common
Thrombocytopenia	Common
Idiopathic thrombocytopenic purpura	Uncommon
Pancytopenia	Rare
Cardiac disorder	
Tachycardia	Common
myocardial infarction	Uncommon
Arrhythmia	Uncommon
Congestive heart failure	Uncommon
Cardiac arrest	Rare
Ear and labyrinth disorders	
Vertigo	Common
Deafness	Uncommon
Tinnitus	Uncommon
Eye disorders	
Visual impairment	Common
Conjunctivitis	Common
Blepharitis	Common
Eye swelling	Common
Diplopia	Uncommon

Gastrointestinal disorders	
Abdominal pain	Very common
Nausea and vomiting	Very common
GI haemorrhage	Common
Dyspepsia,	Common
Gastroesophageal reflux disease	Common
Sicca syndrome	Common
Pancreatitis,	Uncommon
Dysphagia	Uncommon
Face oedema	Uncommon
Intestinal perforation	Rare
General disorders and administration site condition	
Injection site reaction (including injection site erythema)	Very Common
Chest pain	Common
Oedema,	Common
Pyrexia	Common
Inflammation	Uncommon
Hepatobiliary disorders	
Elevated liver enzymes	Very Common
Cholecystitis and cholelithiasis,	Uncommon
Hepatic steatosis,	Uncommon
Bilirubin increased	Uncommon
Hepatitis	Rare
Reactivation of hepatitis	Rare
Autoimmune hepatitis	Rare
Liver failure	Not known

Immune system disorders	
Hypersensitivity	Common

Allergies (including seasonal allergy)	Common
Sarcoidosis	Uncommon
Anaphylaxis	Rare
Metabolism and nutrition disorders	
Lipids increased	Very common
Hypokalaemia	Common
Uric acid increased	Common
Blood sodium abnormal	Common
Hypocalcaemia	Common
Hyperglycaemia	Common
Hypophosphatemia,	Common
Dehydration	Common
Infections and infestations	
Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)	Very common
Systemic infections (including sepsis, candidiasis and influenza)	Very common
Intestinal infections (including gastroenteritis viral)	Very common
Skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster),	Common
Ear infections	Common
Oral infections (including herpes simplex, oral herpes and tooth infections),	Common
Reproductive tract infections (including vulvovaginal mycotic infection)	Common
Urinary tract infections (including pyelonephritis)	Common
Fungal infections	Common
Joint infections	Common

Neurological infections (including viral meningitis)	Uncommon
Opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection)	Uncommon
Bacterial infections	Uncommon
Eye infections	Uncommon
Diverticulitis	Uncommon
Injury, poisoning and procedural complication	
Impaired healing	Common
Investigations	
Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged)	Common
Autoantibody test positive (including double stranded DNA antibody)	Common
Blood lactate dehydrogenase increased	Common
Musculoskeletal and, connective tissue disorders	
Musculoskeletal pain	Very common
Muscle spasms (including blood creatinine phosphokinase increased)	Common
Rhabdomyolysis,	Uncommon
Systemic lupus erythematosus	Uncommon
Lupus-like syndrome	Rare

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma),	Common
Benign neoplasm	Common
Lymphoma	Uncommon
Solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma	Uncommon

Leukaemia	Rare
Hepatosplenic T-cell lymphoma	Not known
Merkel cell carcinoma (neuroendocrine carcinoma of the skin)	Not known
Nervous system disorders	
Headache	Very common
Paraesthesias (including hypoaesthesia)	Common
Migraine,	Common
Nerve root compression	Common
Cerebrovascular accident	Uncommon
Tremor	Uncommon
Neuropathy	Uncommon
Multiple sclerosis	Rare
Demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome)	Rare
Psychiatric disorder	
Mood alterations (including depression)	Common
Anxiety	Common
Insomnia	Common

Renal and urinary disorder	
Renal impairment	Common
Haematuria	Common
Nocturia	Uncommon
Reproductive system and breast disorders	
Erectile dysfunction	Uncommon
Respiratory, thoracic and mediastinal disorder	
Asthma,	Common
Dyspnoea,	Common

Cough	Common
Pulmonary embolism	Uncommon
Interstitial lung disease	Uncommon
Chronic obstructive pulmonary disease	Uncommon
Pneumonitis	Uncommon
Pleural effusion	Uncommon
Pulmonary fibrosis	Rare
Skin and subcutaneous tissue disorders	
Rash (including exfoliative rash	Very Common
Worsening or new onset of psoriasis (including palmoplantar pustular psoriasis	Common
Urticaria	Common
Bruising (including purpura)	Common
Dermatitis (including eczema),	Common
Onychoclasis,	Common
Hyperhydrosis,	Common
Alopecia	Common
Pruritus	Common
Night sweats,	Uncommon
Scar	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Rare
Angioedema	Rare
Cutaneous vasculitis	Rare
Worsening of symptoms of dermatomyositis	Not known
Vascular disorders	
Hypertension	Common
Flushing	Common
Haematoma	Common
Aortic aneurysm	Uncommon
Vascular arterial occlusion	Uncommon

Thrombophlebitis	Uncommon

7.2 Recording Serious Adverse Events and Serious Adverse Reactions

The definition of a serious adverse event (SAE) will be any medical event that:

- Results in death.
- Is life-threatening [refers to an event during which the participant was at risk of death at the time of the event; it does not refer to an event which might have caused death had it been more severe in nature].
- Requires hospitalisation, or prolongation of existing hospitalisation.
- Results in persistent/significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Other important medical events that, based upon appropriate medical judgment, may jeopardise the participant and may require medical or surgical intervention.

All SAEs and Serious Adverse Reactions (SARs) will be recorded in the 'Investigator Site File and the NWORTH trial unit manager will be informed immediately.
The principal investigator or chief investigator at the treatment site will scan and email details of the SAE or SAR to the NWORTH trial unit manager via the NWORTH Sciatic trial manager who will record the information on the trial master file. Following the initial report, all SAEs should be followed up to resolution wherever possible and further information may be requested by NWORTH. The participant will be identified only by the participant's identification number. The participant's name should not be used on any correspondence. Once an SAE is received at NWORTH, it will be evaluated by the CI (or his delegate) for seriousness, expectedness and causality. The causality and expectedness assessment given by the PI cannot be overruled by the CI (or his delegate) and in the case of disagreement; both opinions will be provided with the report.

All SAEs will be reported to the sponsor's representative in Bangor University within 24 hours of being discovered, oversight and pathways for adverse incident reporting during the trial period will be managed by the sponsor's representative within the Healthcare and Medical Sciences Academic Ethics Committee (HCMS AEC) reporting to a standing –committee for trials within the University Ethics Committee (UREC) on behalf of Council. On an annual basis a 'Development Safety Update Report' (DSUR) containing a list of all SAEs and SARs will be submitted to the

MHRA. In addition, all Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the MHRA within seven days (fatal/life threatening) or fifteen days (non-fatal/non-life threatening). They will also be reported to the chair of the DMEC and the research ethics committee. NWORTH will report a list of all SAEs (expected and unexpected) and any other safety recommendations to all PIs every six months, and to the REC every 12 months, throughout the course of the trial. The frequency of PI safety reports may be reviewed and amended as necessary

Training on the adverse events and serious adverse events reporting procedure will be given to all relevant trial staff.

8. Statistics

8.1 Sample Size

From the Weighted Mean Difference (WMD) in our previous meta-analysis we found a relative improvement of eight points in the ODI at six months follow-up in the group receiving biological agents compared with placebo with a standard deviation of 16, giving an effect size of 0.5. In order to detect a more conservative effect size of 0.4 with 90% power, with a significance level of 5% for a two-tailed t test, a sample size of 133 in each treatment group will be needed. We will aim for a 90% return rate of the final questionnaires, but for a more conservative retention rate of 80% 332 will need to be recruited. If, as is likely, there is any correlation between the baseline and outcome measure, the size of effect detectable will be smaller (or the power to detect a 0.4 effect enhanced).

8.2 Recruitment rate

Calculations of recruitment rates for the SCIATiC trial were based on data available from an observational study, led by co-applicants at Keele, which recruited adult patients seeking treatment in primary care for low back-related leg pain including sciatica (ATLAS cohort), the ATLAS study recruited 609 patients from 17 general medical practices (approximate total adult population 90,200) over 24 months. Analysis of the recruitment data shows that 219 (36%) of this cohort had sciatica with pain in one leg only (with >80% diagnostic confidence) with a Roland Morris Disability Questionnaire score >7 (equivalent to ODI≥30). On average per month, 86 potential participants were identified by GP's and referred to the ATLAS study 54 attended the physiotherapy-led research clinic, 25 gave consent and were eligible for the study, nine of whom had a clinical diagnosis of sciatica (spinal nerve root pain) satisfying the condition described above in term of disability score and diagnostic confidence. Based on these figures and taking into account that in the ATLAS cohort, approximately nine participants per month were recruited, and making the

assumption that half this number would consent to be randomised in a RCT, our target rate of recruitment will be four participants per collaborating centre per month with centres covering similar sized populations. For the SCIATiC trial, the collaborating centres will recruit from GP practices with a combined registered population of at least.

8.3 Data analysis

All data will be anonymised and coded so that data collection and statistical analysis will be blinded to treatment allocation. The code will only be broken after the primary analysis has been completed. A full pre-specified SAP will be prepared prior to the data being released to analysts. The analysis will be performed on a 'Treatment as Allocated' principle to ensure protection against unintended bias. The data will be fully imputed using a MICE approach (Multiple Imputation by Chain Equations) [54] in line with the predefined statistical analysis plan to minimise data loss due to missing values or time points. Participants who need to be referred for disc surgery will be labelled as 'treatment failures' and their last test results prior to surgery will be carried forward in the analysis. Sensitivity analyses (best case/worst case) will be performed to assess the influence of different imputation assumptions. All trial reporting will be CONSORT [55] compliant.

8.3.1 Primary analysis

The main outcome variable will be the ODI measured at 12 months. A linear mixed model approach for repeated measures will be used to assess the effects of Time, Group and time*Group will further describe and explain the overall finding (the interaction term will assess whether the effect of the intervention is the same or not at each time point). This model will be fully defined in the SAP prior to all analyses.

8.3.2 Secondary analysis

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 measured from trial entry (this is the date of second consent) and analysed 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). Subgroups will be defined within the SAP prior to analyses beginning.

8.3.3 Economic analysis

The health economic analysis will adopt the perspective of the National Health Service (NHS) and Personal Social Services (PSS) and additionally indirect costs e.g. time off work (secondary analysis). Costs will include those of treatment, tests, procedures and investigations, contact with primary and secondary care services and personal social services. Resource use will be obtained from participants' self-reporting of resource use, captured by questionnaire administration [48, 49]. Unit cost data will be obtained from standard sources such as Curtis [56]. NHS reference costs [57] and other resources such as the BNF [31]. The primary economic outcomes will be the incremental cost per QALY gained, estimated by administering the EQ-5D-5L at each follow-up point. The number of QALYs experienced by each participant will be calculated as the area under the curve, using the trapezoidal rule, applying the UK tariffs and corrected for baseline utility score. Where appropriate, missing resource use or health outcome data will be imputed [57]. Non-parametric bootstrapped 95% confidence intervals will be estimated (10,000 replicates). We will also employ simple parametric approaches for analysing cost and QALY data that assume normal distributions given the large samples where the near-normality of sample means is approximated. Should the data indicate otherwise, we will develop a generalised linear model, to deal with problems such as skewness. Stratified cost-effectiveness analyses will be conducted on important, pre-specified participant subgroups. Total costs will be combined with QALYs to calculate the incremental cost-utility ratio of the package of adalimumab plus physiotherapy compared with 0.9% Sodium Chloride injection plus physiotherapy. Estimates of ICURs will be compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness, and a range of one-way sensitivity analyses will be conducted to assess the robustness of the analysis. Multivariate sensitivity analyses will be applied where interaction effects are suspected. The joint uncertainty in costs and benefits will be considered through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves [58].

9. Trial Management

9.1 Trial Management Group

Individuals responsible for the day-to-day running of the trial will be included in a Trial Management Group (TMG), which will include the chief investigator, principal investigators, trial manager, statistician, health economist, site co-ordinators, research staff, data manager, and collaborating clinicians, as necessary. The TMG's role will be to monitor all aspects of the trial's set-up, conduct and progress. The group will ensure that the protocol is adhered to, and will take appropriate action to

safeguard participants, and ensure the overall quality of the trial. The TMG will report to the DMEC and TSC and will meet every one to two months.

9.2 Trial Steering Committee

A TSC will be set up to oversee the running of the trial on behalf of the sponsor and funder and will have the overall responsibility for the continuation or termination of the trial. The TSC will have an independent chair, a majority of independent members and will include a patient representative. The role of the TSC will be to ensure that the trial is being conducted in accordance with the principles of 'Good Clinical Practice' and the relevant regulations, and will provide advice on all aspects of the trial. The trial protocol and any subsequent amendments will be agreed by the TSC (so this needs to be clear in the timeline listed above). The TSC will report to the TMG, the sponsor and the funder. The TSC will meet every six months.

Trial Steering Committee Members

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9.3 Data Monitoring and Ethical Committee

A DMEC will monitor the progress of the trial and will review all Adverse Events. The DMEC will review results from the internal pilot trial and advise the trial steering committee as needed. It will be able to advise changes to the conduct of the trial or to stop recruitment if it feels the risks of continuing outweigh the benefits. It will be responsible for considering any newly published research data which might affect the trial and any additional information that should be passed on to participants. The trial statistician will be available to answer any questions and to provide blinded and, if requested, unblinded trial data for interim analysis. The TMG will provide regular safety reports to the DMEC. The DMEC will report to and make recommendations to the TSC. It will assess the results of the internal pilot phase of the trial and will inform the funders via the TSC of recommendations arising from those analyses. The DMEC will meet every six months.

Chair
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9.4 Reporting

TMG will report to the DMEC and TSC. The DMEC will report to the TSC and the TSC will report to the TMG, the sponsor and the funder. Safety reports will be submitted every six months to the REC, the sponsor and the funder. Development update safety reports will be submitted to the MHRA.

10. Direct Access to Source Data and Documents

Source data will be the hospital written and NHS electronic medical records. Access to this data will be through the participant's clinicians, physiotherapist and research nurse. Trial related monitoring, audits, Research Ethics Committee reviews and regulatory compliance inspections will be permitted, allowing access to data and documents where required. It is intended to develop data recording for this trial as a web based system. This is a secure encrypted system accessed by an individual password, and complies with Data Protection Act standards

11. Ethics & Regulatory Approvals

Applications will be made for research ethics committee and NHS research and development approvals via the on-line Integrated Research Application System (IRAS). Clinical Trial Authorisation will be sought from the MHRA. All trial data, including participant information sheets, participant consent forms, template GP letters, and questionnaires will be submitted for approval. To conform to the Data Protection Act and Freedom of Information Act, all data will be anonymised and stored securely. No published material will contain participant identifying information. If new evidence becomes available during the course of the trial, for example suggesting that the intervention is substantially better or worse than usual care, it is the responsibility of the DMEC to consider such issues and make recommendations on the continuation of the trial to the TMG.

12. Quality Assurance

This trials will be conducted in line with the trial protocol and will follow the principles of good clinical practice outlined by the ICH- GCP E6 (R1) and will comply with the EU directive 2001/20/EC.

A monitoring plan will be developed based on a trial risk assessment, which will provide details of day to day quality control, audits, etc., and will be delegated to members of the trial team to ensure that collected data adhere to the requirements of the protocol; only authorised persons complete Case Report Forms (CRFs); the potential for missing data is minimised; data are valid through validation checks (e.g.

range and consistency checks); recruitment rates, withdrawals and losses to follow-up are reviewed overall and by hospital site. The process of data analysis will include appropriate methods for ensuring the findings are plausible and credible.

13. Data Handling

The sources of data for the trial will be as follows: recruitment details, baseline outcome measures captured electronically onto password protected and encrypted computers by the research physiotherapists or research nurses, postal questionnaires at six weeks, six and twelve months scanned into the Macro © system, telephone minimum data collection from non-responders captured on computers by researchers. Additional health service use data obtained from primary and secondary care records, with participants' consent, will be recorded electronically on the computers. Each centre will input data into the Macro © data management programme, which is a web-based system allowing controlled access to data by all centres and allows a full audit trail. The procedures regarding coding specification, review of the data, cleaning process for the data and freezing the final dataset for analysis will be as described in NWORTH SOPs.

14. Publication Policy

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, and 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 on-line patient materials.

15. Financial Aspects

The trial is funded by a grant from the NIHR Health Technology Assessment awarded to Bangor University, and will be managed in accordance with the relevant policies and procedures. Bangor University has appropriate Clinical Trials Indemnity and Professional Indemnity insurance in place that will cover members of the research team to conduct the research as per protocol. NHS staff who work with participants involved in the intervention will not be expected to do anything that is not covered by their contracts and will remain covered by the NHS insurance arrangements

16. Approval signatures

Chief Investigator Signature: ..... Date:……

Print name: *Dr Nefyn Williams*

Statistician Signature: ..... Date: .....

Print name *Dr Zoe Hoare*

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