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Abstract

Subcutaneous Injection of Adalimumab Trial compared with Control (SCIATiC): a randomised controlled trial of adalimumab injection compared with placebo for patients receiving physiotherapy treatment for sciatica

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Background: Biological treatments such as adalimumab (Humira®; AbbVie Ltd, Maidenhead, UK) are antibodies targeting tumour necrosis factor alpha, released from ruptured intervertebral discs, which might be useful in sciatica. Recent systematic reviews concluded that they might be effective, but that a definitive randomised controlled trial was needed. Usual care in the NHS typically includes a physiotherapy intervention.

Objectives: To test whether or not injections of adalimumab plus physiotherapy are more clinically effective and cost-effective than injections of saline plus physiotherapy for patients with sciatica.

Design: Pragmatic, parallel-group, randomised controlled trial with blinded participants and clinicians, and an outcome assessment and statistical analysis with concurrent economic evaluation and internal pilot.

Setting: Participants were referred from primary care and musculoskeletal services to outpatient physiotherapy clinics.

Participants: Adults with persistent symptoms of sciatica of 1–6 months' duration and with moderate to high levels of disability. Eligibility was assessed by research physiotherapists according to clinical criteria for diagnosing sciatica.

Interventions: After a second eligibility check, trial participants were randomised to receive two doses of adalimumab (80 mg and then 40 mg 2 weeks later) or saline injections. Both groups were referred for a course of physiotherapy.

Main outcome measures: Outcomes were measured at the start, and after 6 weeks' and 6 months' follow-up. The main outcome measure was the Oswestry Disability Index (ODI). Other outcomes: leg pain version of the Roland–Morris Disability Questionnaire, Sciatica Bothersomeness Index, EuroQol-5 Dimensions, 5-level version, Hospital Anxiety and Depression Scale, resource use, risk of persistent disabling pain, pain trajectory based on a single question, Pain Self-Efficacy Questionnaire, Tampa Scale of Kinesiophobia and adverse effects.

Sample size: To detect an effect size of 0.4 with 90% power, a 5% significance level for a two-tailed *t*-test and 80% retention rate, 332 participants would have needed to be recruited.

Analysis plan: The primary effectiveness analysis would have been linear mixed models for repeated measures to measure the effects of time and group allocation. An internal pilot study would have involved the first 50 participants recruited across all centres. The primary economic analysis would have been a cost–utility analysis.

Results: The internal pilot study was discontinued as a result of low recruitment after eight participants were recruited from two out of six sites. One site withdrew from the study before recruitment started, one site did not complete contract negotiations and two sites signed contracts shortly before trial closure. In the two sites that did recruit participants, recruitment was slow. This was partly because of operational issues, but also because of a low rate of uptake from potential participants.

Limitations: Although large numbers of invitations were sent to potential participants, identified by retrospective searches of general practitioner (GP) records, there was a low rate of uptake. Two sites planned to recruit participants during GP consultations but opened too late to recruit any participants.

Conclusion: The main failure was attributable to problems with contracts. Because of this we were not able to complete the internal pilot or to test all of the different methods for primary care recruitment we had planned. A trial of biological therapy in patients with sciatica still needs to be done, but would require a clearer contracting process, qualitative research to ensure that patients would be willing to participate, and simpler recruitment methods.

Trial registration: Current Controlled Trials ISRCTN14569274.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 21, No. 60. See the NIHR Journals Library website for further project information.

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List of abbreviations

ATLAS	Assessment and Treatment of Leg pain Associated with the Spine
BCUHB	Betsi Cadwaladr University Health Board
CI	confidence interval
CrI	credible interval
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol-5 Dimensions, 5-level version
ETC	excess treatment cost
GP	general practitioner
HTA	Health Technology Assessment
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
ODI	Oswestry Disability Index
OR	odds ratio
PI	principal investigator
PSEQ	Pain Self-Efficacy Questionnaire
QALY	quality-adjusted life-year
R&D	research and development
RCT	randomised controlled trial
REC	Research Ethics Committee
RMDQ	Roland–Morris Disability Questionnaire
SCIATiC	Subcutaneous Injection of Adalimumab Trial compared with Control
SCOPiC	Sciatica Outcomes in Primary Care
TB	tuberculosis
TMG	Trial Management Group
TNF-α	tumour necrosis factor alpha
TSC	Trial Steering Committee
WMD	weighted mean difference

Plain English summary

Sciatica is a severe leg pain usually caused by inflammatory chemicals released from a ruptured intervertebral disc irritating a nerve as it leaves the spine. Biological treatments such as adalimumab (Humira®, AbbVie Ltd, Maidenhead, UK) block the effects of these chemicals and may be effective for treating sciatica.

We aimed to test whether or not adalimumab injections plus physiotherapy are more effective, and better value for money, than saline injections plus physiotherapy for patients with sciatica.

Participants were adults with sciatica for 1–6 months and with moderate or high disability. They were referred from primary care and musculoskeletal services to outpatient physiotherapy clinics. They received, at random, either two doses of adalimumab or saline injections. Both groups were referred for a course of physiotherapy treatment.

Outcomes were measured at the start, and after 6 weeks' and 6 months' follow-up. The main outcome was back pain-related disability. Other outcomes measured leg pain disability, bothersomeness, general health, anxiety, depression, resource use, predictors of disability and adverse effects.

We planned to recruit 332 participants, with the first 50 taking part in a pilot study. Unfortunately, only eight participants were recruited from two out of six sites. Of the other four sites, one dropped out, one failed to complete contract negotiations and two did not sign their contracts until just before trial closure. In the two sites that did recruit participants, large numbers of invitations were sent, but uptake was poor. Two sites planned to recruit participants during general practitioner consultations but opened too late to recruit.

The research question is still an important one to answer. A number of factors contributed to poor recruitment: contracts, inefficient identification of participants, delays in site set-up and lack of investigator engagement. Because of this, we were not able to complete the internal pilot or test all of the different methods for primary care recruitment that we had planned.

Scientific summary

Background

Sciatica is a severe leg pain usually caused by a ruptured intervertebral disc, the contents of which compress and irritate a lumbar nerve root. It is common, disabling and costly to the health service and to society. Current care pathways in the NHS typically involve the prescribing of analgesia by the patient's general practitioner (GP) and, if troublesome symptoms persist, referral for physiotherapy 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 5–15% of patients eventually need disc surgery.

Sciatica caused by lumbar nerve root pain is usually caused by a prolapsed intervertebral disc, not only because of compression of the nerve root, but also as a result of the release of proinflammatory factors from the damaged disc, such as tumour necrosis factor alpha (TNF-α). Biological agents, such as the monoclonal antibodies infliximab (AbbVie, Maidenhead, UK) and adalimumab (Humira®, AbbVie Ltd, Maidenhead, UK), bind specifically to TNF-α receptors and may have beneficial effects on the inflamed nerve root in sciatica. A network meta-analysis of different treatment strategies for sciatica found that biological agents had the highest probability of being best, but with wide confidence intervals. A meta-analysis of biological agents for sciatica compared with placebo combined six randomised controlled trials (RCTs) and one non-RCT, and found that biological agents resulted in reduced leg pain intensity in the short term and increased global effects in the medium term. However, these findings were no longer statistically significant when studies were restricted to RCTs. Although there was insufficient evidence to change practice from these reviews, there was sufficient evidence to suggest that a definitive RCT was warranted. This systematic review did not identify any economic evaluations. Although these treatments are costly, they may be cost-effective if they reduce the need for more expensive treatments such as disc surgery. In addition, when their patent expires, cheaper biosimilar drugs may be developed and used in their place. Adalimumab is administered by subcutaneous injection, but infliximab confers the additional expense of intravenous injection. We used adalimumab because of its ease of administration and, in order to provide a therapeutic effect lasting 1 month, two subcutaneous injections were given 2 weeks apart. In order to initiate a rapid response, we used the typical starting dosage when treating psoriasis or Crohn's disease of 80 mg followed by 40 mg.

Objectives

1. To evaluate the clinical effectiveness of subcutaneous injections of adalimumab plus physiotherapy compared with a placebo injection of 0.9% sodium chloride plus physiotherapy for patients with sciatica in whom first-line primary care treatment had failed. We planned to identify potential participants during primary care consultation, after referral to musculoskeletal service or following a practice database search.
   The primary effectiveness outcome was sciatica-related health status using the Oswestry Disability Index (ODI). Secondary effectiveness outcomes included pain intensity, location, duration and anticipated trajectory; the risk of poor outcome; psychological measures including fear of movement, self-efficacy, anxiety and depression; employment status; and adverse effects.
2. To evaluate, from a health service and personal social care perspective, the cost-effectiveness of subcutaneous injections of adalimumab plus physiotherapy compared with a placebo injection of 0.9% sodium chloride plus physiotherapy for patients with sciatica in whom first-line primary care treatment had failed. The primary economic outcome was the incremental cost per quality-adjusted life-year (QALY) gained. QALYs would be estimated by administering the EuroQol-5 Dimensions, 5-level version (EQ-5D-5L) at each follow-up visit.

Methods

Design

Pragmatic, multicentre RCT with blinded participants and clinicians, and an outcome assessment and statistical analysis with concurrent economic evaluation and internal pilot.

Main centres

The RCT aimed to recruit from six sites overseen by five collaborating centres in North Wales, London, Keele, Nottingham and Cardiff.

Selection and withdrawal of subjects

Each collaborating centre would oversee a number of patient identification centres, which consisted of general medical practices and local musculoskeletal services. Patients would be identified in three ways:

1. by their GP
2. following a search of the general practice patient record database
3. after referral to local musculoskeletal services.

Research clinic

Patients were invited to participate by letter. Those who were interested were contacted by telephone and, if they fitted the inclusion criteria, were given an appointment in a research clinic run by a research physiotherapist. At this research clinic all potential participants were assessed by the research physiotherapist for eligibility. If eligible, participants had blood tests, tuberculosis screening, biological agents counselling and magnetic resonance imaging (MRI) to exclude serious spinal pathology. A second clinical assessment by the research physiotherapist 2–3 weeks later assessed if they were still eligible. If they were, informed consent was obtained for trial entry and randomisation.

Inclusion criteria

- Aged ≥ 18 years.
- Clinical features of sciatica.
- Leg pain worse or as bad as back pain.
- Unilateral leg pain approximating a dermatomal distribution (contralateral buttock pain permitted if it did not extend below the inferior gluteal margin).
- One of the following:
    - positive neural tension test, such as the straight-leg raise test restricted to < 50° 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 < 6 months despite first-line treatment in primary care.
- Moderate to high severity (score of ≥ 30 points) on the ODI.
- Female partners of sexually active male participants should use adequate contraceptives for at least 5 months after the last injection. Female participants should have a negative urine pregnancy test within 2 weeks prior to randomisation, unless they were post menopause or had had a sterilisation operation. Sexually active men of female participants must also use adequate contraceptive methods.

Exclusion criteria

- Unable to perform MRI.
- Serious spinal pathology.
- Incidental serious pathology identified by MRI.

- Neurological deficit involving muscle weakness requiring an urgent spinal surgery assessment (e.g. foot drop).
- Widespread pain throughout the body including the upper limb.
- Prior use of biological agents targeting TNF-α within the previous 6 months.
- Previous lumbar spinal surgery.
- Contraindications to adalimumab injection, including serious infection such as active or latent tuberculosis, transplanted organ, demyelinating disorders, malignancy, cardiac failure, low white cell count and pregnancy.
- Pregnancy or breastfeeding (women must not breastfeed for at least 5 months after the last adalimumab injection).
- Unable to communicate in English or Welsh.
- Unable or unwilling to give informed consent.

Randomisation

Randomisation was achieved by secure web access to the remote randomisation system at the North Wales Organisation for Randomised Trials in Health at Bangor University, and was performed by a dynamic adaptive randomisation algorithm to protect against subversion while ensuring that the trial maintained good balance to the allocation ratio of 1 : 1 both within each stratification variable and across the trial. Participants were stratified by (1) treatment centre and (2) presence of neurological signs (motor weakness or sensory loss).

Subcutaneous injections

All participants were randomised to receive two doses of subcutaneous injection 2 weeks apart in the posterior thigh. The intervention group received 80 mg of adalimumab followed by 40 mg. The control group received 0.9% sodium chloride in an equivalent volume to the intervention group.

Concurrent physiotherapy

Both groups received a concurrent course of physiotherapy provided over a period of 12 weeks. The number of sessions provided was determined by participant and therapist preference, and also response to treatment. We aimed to capture and describe these aspects of physiotherapy treatment as part of the trial.

Clinical management of persistent symptoms

Once the participants had completed their course of physiotherapy, if their symptoms had settled or were improving, no further intervention was organised. They were discharged to the care of their GP and followed up by the research team as described in this protocol. If troublesome symptoms persisted, then further treatment was planned as appropriate by referral to musculoskeletal interface clinics or secondary care specialists according to local arrangement in each of the centres.

Internal pilot trial

This aimed to rehearse the procedures and logistics to be undertaken in the main trial. It would assess the feasibility of the arrangements for delivering the interventions, recruitment rate and initial retention rate. The internal pilot was based on the first 50 participants recruited into the trial. The stopping criteria at the end of this internal pilot would be recruitment that failed to reach 80% of the planned recruitment rate target, dropouts up until the 6-week postal questionnaire assessment exceeding 20%, or more than one centre failing to commence recruitment.

Primary outcome

The primary clinical outcome was back pain-specific disability using the ODI, measured at 12 months. The primary economic outcome was the incremental cost per QALY gained, estimated by administering the EQ-5D-5L at each follow-up visit.

Outcome measures

Condition-specific outcomes

- Back pain-specific disability using the ODI.
- Leg pain-related functional disability using the leg pain version of the Roland–Morris Disability Questionnaire.
- Leg pain interference using the Sciatica Bothersomeness Index.
- Pain location using a pain manikin.

Generic outcomes

- Health utility using the EQ-5D-5L.
- Global assessment of change since baseline.

Psychological outcomes

- Anxiety and depression using the Hospital Anxiety and Depression Scale.

Use of health care and social care services

- Resource Use Questionnaire.

Process measures (potential predictors and mediators of outcome)

- Risk of persistent disabling pain (STarT Back screening tool).
- Pain trajectory (based on a single question).
- Pain Self-Efficacy Questionnaire.
- Fear avoidance beliefs (Tampa Scale of Kinesiophobia).

Follow-up

The outcomes would be collected at baseline, and after 6 weeks', 6 months' and 12 months' follow-up. The baseline was administered by research physiotherapists. We would send postal questionnaires at 6 weeks' and at 6 and 12 months' follow-up.

Statistics

Sample size

From the weighted mean difference in our previous meta-analysis, we found a relative improvement of 8 points in the ODI at 6 months' follow-up in the group receiving biological agents compared with placebo, with a standard deviation of 16 points, giving an effect size of 0.5. 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 would be needed. We aimed for a 90% return rate of the final questionnaires, but for a more conservative retention rate of 80%, 332 participants would need to be recruited.

Data analysis

All data were anonymised and coded so that data collection and statistical analysis would be blinded to treatment allocation and performed on a 'treatment as allocated' principle.

The main outcome variable would be the ODI measured at 12 months. A linear mixed-model approach for repeated measures would be used to assess the effects of time, group and time × group. Secondary continuous outcome variables would be assessed in a similar way, with the exception of time to referral for surgery, which would be assessed from trial entry (this is the date of second consent) using Kaplan–Meier

survival analyses and the log-rank test. Dichotomous variables would be explored using logistic regression. These analyses would be repeated using prespecified participant subgroups (including the presence of neurological deficit on entry to the trial and MRI findings).

Economic analysis

The health economic analysis would adopt the perspective of the NHS and personal social services and, additionally, indirect costs [e.g. time off work (secondary analysis)]. Costs would include those of treatment, tests, procedures and investigations, and contact with primary and secondary care services and personal social services. Resource use would be obtained from participants' self-reporting of resource use, captured by questionnaire administration. Unit cost data would be obtained from standard sources. The primary economic outcomes would be the incremental cost per QALY gained, estimated by administering the EQ-5D-5L at each follow-up point. Non-parametric bootstrapped 95% confidence intervals would be estimated (10,000 replicates). Total costs would be combined with QALYs to calculate incremental cost–utility ratios. Estimates of incremental cost-effectiveness ratios would be compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness, and a range of one-way sensitivity analyses would be conducted to assess the robustness of the analysis. Multivariate sensitivity analyses would be applied when interaction effects were suspected. The joint uncertainty in costs and benefits would be considered through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves.

Results

Following initial delays finalising the trial contract with the funder, approvals were obtained with only small delays in the timetable. There were much longer delays negotiating subcontracts with sites. The contract negotiation in one site was never completed because of ongoing discussion about roles and responsibilities, and one site withdrew because the principal investigator had safety concerns of the initial dose. Only two sites recruited participants. In one site there were delays in recruiting from secondary care populations and delays in setting up primary care recruitment. In the other site, there were delays setting up the site, difficulties recruiting research physiotherapists and a poor rate of recruitment following the postal invitation to participate.

Although large numbers of invitations were sent to potential participants ($n = 1546$), there was a low rate of uptake with only 25 patients (2%) seen for an initial assessment, and eight patients (32%) were entered into the trial. Recruitment was improving just before the trial was closed, with five potential participants ready to be recruited within the following month.

Conclusions

The research question is still important to answer but, because of the lack of trial results, we cannot make any recommendations for future practice. The main failure was as a result of problems with contracts. Because of this, we were unable to complete the internal pilot study. There may be insufficient equipoise around the question of adalimumab for sciatica among patients and some clinicians, which could be addressed with qualitative research. The two-stage recruitment process was complicated and not feasible. We had planned to test other methods of primary care recruitment, but unfortunately the trial closed before we were able to do so.

A trial of biological therapy in patients with sciatica still needs to be done, but would require a clearer contracting process, qualitative research to ensure that patients would be willing to participate and simpler recruitment methods.

Trial registration

This trial is registered as ISRCTN14569274.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Sciatica is a symptom defined as unilateral, well-localised leg pain, with a sharp, shooting or burning quality, which 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% of patients having persistent troublesome symptoms at 1 year, with 20% of the total out of work.[3,4] However, another cohort found that 55% still had symptoms of sciatica 2 years later, and 53% after 4 years (which included 25% who had recovered after 2 years but had relapsed again by 4 years).[5] Current care pathways in the NHS typically involve the prescribing of analgesia by the patient's general practitioner (GP) 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% and 15% of patients with sciatica undergo disc surgery.[3,4] In the NHS in England in 2013/14, 8330 lumbar discectomies were performed.[8] Based on a Dutch trial that indicated that the cost of sciatica to society represents 13% of all back pain-related costs, the annual impact on the UK economy is £268M in direct medical costs and £1.9B 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 proinflammatory 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 (MRI) 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 randomised controlled trials (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.[7,15–17] 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 proinflammatory factor released from the prolapsed intervertebral disc is tumour necrosis factor alpha (TNF-α).[11,12] The monoclonal antibodies infliximab and adalimumab (Humira®; AbbVie Ltd, Maidenhead, UK) target TNF-α 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-α receptors on the cell surface and modulate biological responses that are induced or regulated by TNF-α, including the inflammatory process.[18] They may also have beneficial effects on the inflamed nerve root in sciatica,[19] and have the additional advantage of being administered by intravenous (infliximab) or subcutaneous (adalimumab) injection in a hospital outpatient clinic, rather than by epidural injection as a hospital day case.

This research followed the recommendations of a Health Technology Assessment (HTA)-funded systematic review of management strategies for sciatica.[20] 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 pairwise 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, with an odds ratio (OR) compared with inactive control of 16, but with very wide 95% credible intervals (CrIs) of 0.6 to 1002, reflecting the small number of

included studies and lack of data that were available to inform these effect estimates. A CrI is a Bayesian confidence interval (CI). 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), and were found to be statistically significantly better than the inactive control, but with wide CrIs, with a weighted mean difference (WMD) of –22 (95% CrI –36 to –8) compared with an opioid WMD of –31 (95% CrI –53 to –9) and a non-opioid analgesia WMD of –18 (95% CrI –33 to –2).

Following this HTA review we updated the literature search of biological agents for sciatica (from inception to February 2012).[21] 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 6 weeks' follow-up) (OR 2.0, 95% CI 0.7 to 6.0), medium term (around 6 months' follow-up) (OR 2.7, 95% CI 1.0 to 7.1) and long term (≥ 12 months' follow-up) (OR 2.3, 95% CI 0.5 to 9.7); improved leg pain intensity in the short term (WMD –13.6, 95% CI –26.8 to –0.4) and medium term (WMD –7.0, 95% CI –15.4 to 1.5), but not the long term (WMD 0.2, 95% CI –20.3 to 20.8); and improved Oswestry Disability Index (ODI) score 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 intravenous corticosteroids (one historical cohort trial),[29] but not compared with epidural corticosteroid (two RCTs).[27,30] We concluded that there was some evidence of efficacy, but a paucity of evidence for clinical effectiveness for biological agents. Although there was insufficient evidence to change practice, there was sufficient evidence to suggest that a definitive RCT was warranted.

As part of the HTA review of management strategies for sciatica,[20] 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 for whom primary care treatment has failed, with the potential to reduce the need for more invasive treatments.

In summary, 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,[31] there have been no economic evaluations of these agents. Although they might be beneficial for patients with sciatica, these agents are expensive costing £352 for 40 mg of adalimumab and £420 for 100 mg of infliximab.[32] Adalimumab is administered by subcutaneous injection, but infliximab confers the additional expense of intravenous injection. We intended to use adalimumab because of its ease of administration and, in order to provide a therapeutic effect lasting 1 month, two subcutaneous injections would be given 2 weeks apart. In order to initiate a rapid response, we used the typical starting dosage when treating psoriasis or Crohn's disease of 80 mg followed by 40 mg.[18] 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 £3676 and £4971.[32] When the patent for adalimumab expires, it may result in the development of cheaper biosimilar drugs that can be used in its place. From searches of databases of current trials (inception to November 2013), we have not identified any large RCTs with a concurrent economic evaluation in a NHS setting.

Trial objectives

1. To evaluate the clinical effectiveness of subcutaneous injections of adalimumab plus physiotherapy compared with a placebo injection of 0.9% sodium chloride plus physiotherapy for patients with sciatica who have failed first-line primary care treatment. Potential participants were planned to be identified during primary care consultation, after referral to musculoskeletal service or following a practice database search.
   The primary effectiveness outcome was sciatica-related health status using the ODI.[33] Secondary effectiveness outcomes included 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; and adverse effects.
2. To evaluate the cost-effectiveness of subcutaneous injections of adalimumab plus physiotherapy compared with a 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 was the incremental cost per quality-adjusted life-year (QALY) gained. QALYs would be estimated by administering the EuroQol-5 Dimensions, 5-level version (EQ-5D-5L)[34] at each follow-up visit.

Trial flow

The flow chart to show the different stages of the trial is presented in *Figure 1*. The flow chart to show the experience of the participant through the trial is in *Figure 2*.

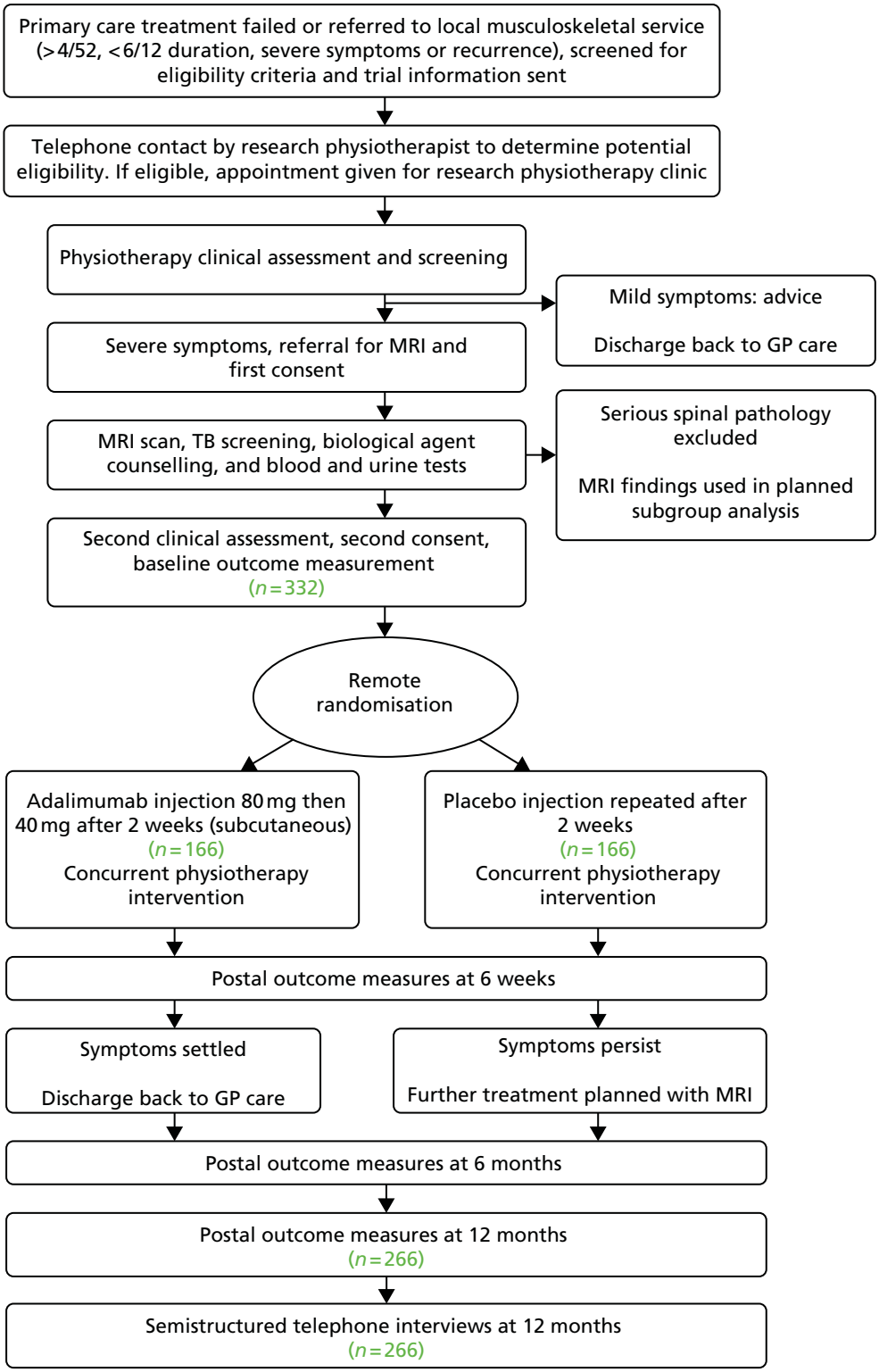

FIGURE 1 Consolidated Standards of Reporting Trials flow chart. MRI, magnetic resonance imaging; TB, tuberculosis.

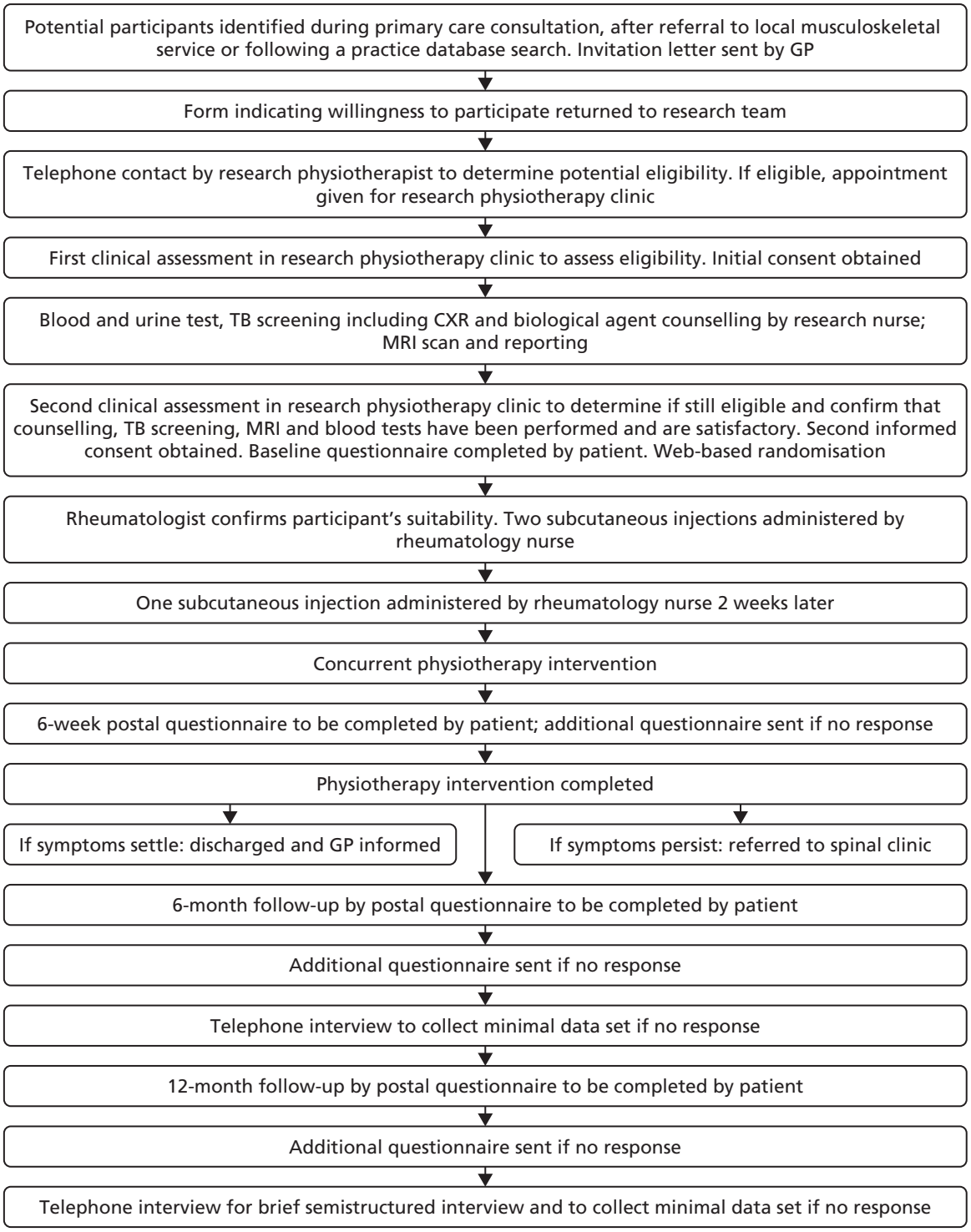

FIGURE 2 Participant flow chart. CXR, chest radiography; MRI, magnetic resonance imaging; TB, tuberculosis.

Chapter 2 Methods

Design

Pragmatic, multicentre RCT with blinded participants, clinicians, outcome assessment and statistical analysis with concurrent economic evaluation and internal pilot.

Main centres

The RCT was planned to recruit from sites overseen by five collaborating centres in North Wales, London, Keele, Nottingham and Cardiff.

Selection and withdrawal of participants

Each collaborating centre oversaw one or more treatment sites that were delegated responsibility for delivering the interventions. Each treatment site had a number of patient identification centres, which consisted of general medical practices and local musculoskeletal services. The target population was adults with suspected sciatica for whom primary care treatment had failed. This was defined as troublesome symptoms (e.g. back and leg pain, pins and needles, numbness in leg, weakness), persisting for > 4 weeks and < 6 months. As the recruitment process took at least 4 weeks before participants were randomised, we did not have a lower time limit for duration of symptoms when identifying the target population and had an upper time limit of 20 weeks. These patients were identified in three ways:

1. by their GP
2. following a search of the general practice patient record database
3. after referral to local musculoskeletal services.

General practitioner referral

Patients identified during the primary care consultation with suspected sciatica were 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 North Wales and Keele, the primary care database displayed 'pop-up' screen messages to remind GPs about the study when potential patients were consulted.

Following a search of the general practice patient record database

Potential participants were identified by regular searches of the general practice patient record database by the practice management staff, directed by research officers from either the Health and Care Research Wales workforce or the local Clinical Research Network in England. The database was searched for diagnostic codes for sciatica. Participants were excluded if they had a known serious spinal pathology or a contraindication to adalimumab injection, such as serious infection [e.g. active or latent tuberculosis (TB)], transplanted organ, demyelinating disorders, malignancy, cardiac failure, low white blood cell count or pregnancy. Those identified as potentially eligible were invited to participate by a written invitation from their GP on the practice's headed notepaper, and hand signed by a GP. Those who were interested returned the reply slip to the research team in the pre-paid envelope.

Local musculoskeletal services

Potential participants with suspected sciatica were also identified from referrals to local musculoskeletal services. Those identified were invited to participate by a written invitation from the local service on headed notepaper. Those who were interested returned the reply slip to the research team in the pre-paid envelope.

The centres in North Wales, Keele and Cardiff planned to identify and recruit participants in three ways: by their GP, following a search of the general practice patient record database or after referral to local musculoskeletal services. Nottingham and London planned to recruit and identify participants who had been referred to their local musculoskeletal services.

Telephone contact by the research physiotherapist

All those who had contacted the research team to state that they were interested in participating were sent a participant information sheet and were contacted by telephone by the research physiotherapist. The telephone call determined if they had unilateral leg pain and, if back pain was present, that leg pain intensity was worse than, or as bad as, the back pain. It also determined whether or not symptoms had persisted for > 20 weeks (to allow participants to be within the 6-month limit at randomisation). Finally, the telephone call allowed them to discuss any questions that they may have had about the study or their symptoms.

Research clinic

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

- demographic details such as age, sex, 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, pinprick and light-touch sensation, quadriceps and Achilles tendon reflexes.

The research physiotherapist arranged for the participant to have the following blood tests taken by the phlebotomist to exclude haematological and biochemical abnormalities: full blood count, urea and electrolytes, estimated glomerular filtration rate, liver function test and glycosylated haemoglobin. The participant received TB screening in accordance with local practice and biological agents counselling. The research physiotherapist then arranged an appointment for MRI to exclude serious spinal pathology. All of these tests were completed within 2–3 weeks of the initial clinic visit and were recorded on the case report forms. The presence or absence of a disc prolapse on MRI was not to 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] MRI was reported by the local radiologist using a trial-specific standard operating procedure. The initial report stated whether or not the participant had serious spinal pathology that required a different treatment. A full MRI report was available only after completion of the study. Individual results were made available if a report was needed in an emergency, or if a spinal surgery referral was contemplated.

The research physiotherapist ensured that the participant received all the required tests. If there was any issue that required action, then the participant's referring GP or musculoskeletal clinician was informed. When MRI had excluded serious spinal pathology, participants were contacted by the research physiotherapists either by telephone or post to attend the research clinic, where they received a second clinical assessment by the research physiotherapist, 2–3 weeks after their initial visit, to assess if they were still eligible. If they were still eligible, further consent was obtained for trial entry and randomisation when they were provided with a unique participant identification number. *Table 1* shows the schedule of forms and procedures.

TABLE 1 The Subcutaneous Injection of Adalimumab Trial compared with Control (SCIATiC) protocol schedule of forms and procedures

	Study period				Follow-up period		
Time point	Enrolment	Randomisation (within 2–3 weeks of registration)	Treatment visit 1 (within 3 days of randomisation)	Treatment visit 2	6 weeks	6 months	12 months
Eligibility	✗	✗					
Informed consent	✗	✗					
Registration to trial	✗						
FBC	✗						
Urine pregnancy test	✗						
U&E	✗						
TB screening	✗						
MRI	✗						
MRI reporting[a]	✗[a]						✗[a]
Eligibility confirmed	✗	✗					
Randomisation		✗					
Subcutaneous injection of allocated treatment			✗	✗			
Physiotherapy treatment				✗	✗		
ODI		✗			✗	✗	✗
EQ-5D-5L		✗			✗	✗	✗
RMDQ		✗			✗	✗	✗
SBI		✗			✗	✗	✗
STarT Back Screening Tool		✗					
PSEQ		✗			✗	✗	✗
HADS		✗			✗	✗	✗
TSK		✗			✗	✗	✗

continued

TABLE 1 The Subcutaneous Injection of Adalimumab Trial compared with Control (SCIATiC) protocol schedule of forms and procedures (*continued*)

	Study period				Follow-up period		
Time point	Enrolment	Randomisation (within 2–3 weeks of registration)	Treatment visit 1 (within 3 days of randomisation)	Treatment visit 2	6 weeks	6 months	12 months
RUQ		✗			✗	✗	✗
Pain outcome		✗			✗	✗	✗
Manikin pain diagram		✗			✗	✗	✗
Pain duration		✗					
Pain trajectory		✗					
Days of work		✗			✗	✗	✗
Global assessment of change					✗	✗	✗
Adverse events		✗	✗	✗	✗	✗	

FBC, full blood count; HADS, Hospital Anxiety and Depression Scale; PSEQ, Pain Self-Efficacy Questionnaire; RMDQ, Roland–Morris Disability Questionnaire; RUQ, Resource Use Questionnaire; SBI, Sciatica Bothersomeness Index; TSK, Tampa Scale of Kinesiophobia; U&E, urea and electrolytes.

a The findings of the MRI will only be available to the participant's 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.

Inclusion criteria

- Aged ≥ 18 years.
- Clinical features of sciatica.
- Leg pain worse or as bad as back pain, elicited by asking the participant.
- Unilateral leg pain approximating a dermatomal distribution (contralateral buttock pain permitted if it did not succeed the inferior gluteal margin), obtained by asking the participant.
- One of the following:
    - positive neural tension test, such as straight-leg raise test restricted to < 50° 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 < 6 months despite first-line treatment in primary care, obtained by asking the participant.
- Moderate to high severity (score of ≥ 30 points on the ODI).[33]

Female partners of sexually active male participants had to use adequate contraception for at least 5 months after the last injection. Female participants were required to have had a negative urine pregnancy test within 2 weeks prior to randomisation, unless they were post menopause or had been sterilised. Sexually active male partners of female participants were also required to use adequate contraceptive methods. The researcher ensured that the risks, and consequences, of not using adequate contraception were fully understood by the participants and provided information and pathways as deemed necessary.

Exclusion criteria

- Symptoms persisting for > 6 months (elicited by asking the participant).
- A previous episode of sciatica in the last 6 months.
- Unable to undergo MRI (e.g. magnetic metal implants, potential metallic intraocular 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 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 was considered widespread when all of the following were 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. Axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) had also to be present.
- Prior use of biological agents targeting TNF-α within the previous 6 months obtained from the medical records and by asking the participant.
- Previous lumbar spinal surgery, elicited from the medical records and by asking the participant.
- Contraindications to adalimumab injection including serious infection such as active or latent TB, transplanted organ, demyelinating disorders, malignancy, cardiac failure, low white blood cell count, pregnancy (determined from the medical records, the results of investigations and by asking the participant).
- Pregnant or breastfeeding (women must not breastfeed for at least 5 months after the last adalimumab injection).
- Unable to communicate in English or Welsh.
- Unable or unwilling to give informed consent.

Informed consent

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

Eligible participants who gave initial consent had blood tests to exclude haematological and biochemical abnormalities (full blood count, urea and electrolytes, estimated glomerular filtration rate, liver function test, glycated haemoglobin levels). They received TB screening, including plain chest radiography, biological agents counselling and MRI to exclude serious spinal pathology within 2–3 weeks of their initial visit. When MRI had excluded serious spinal pathology, and TB screening, a pregnancy test (in the case of eligible women) and biological agent counselling had been completed, participants attended a further appointment with the research physiotherapist. A second clinical assessment was performed and those who were still eligible were asked to complete a second informed consent form, approved by the ethics committee. In order to enter the RCT, the participant was randomised by the research physiotherapist using a remote web-based system. The treatment site sent a letter to each participant's GP, informing them of their patient's participation in the trial and requesting that the GP make a note of this in the patient's record. In addition, GPs were asked to inform the trial team if they became aware that the participant had experienced an adverse event during the trial.

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

Magnetic resonance imaging

Participants who had given initial informed consent underwent MRI to exclude serious spinal pathology, but the presence or absence of a disc prolapse was not used as an inclusion criterion. The MRI scans were read and reported by a local radiologist, using a trial-specific standard operating procedure at each treatment site, who was independent of the trial team. Only results that showed serious pathology or suspected serious pathology were revealed to the research team, referring GP and the musculoskeletal clinician, who would then exclude the participant and refer for urgent assessment. Otherwise, the research team were informed that no serious spinal pathology was identified. The findings of MRI would be made available to the participant's treating clinician only after completion of the study. Individual results were made available if a report was needed in an emergency, or if a spinal surgery or epidural injection referral was being contemplated, and were distributed to the clinical team, referring GP and the musculoskeletal clinician. The MRI findings were to be used in a planned a priori subgroup analysis. For clinical purposes, radiologists from each site provided a clinical report of the MRI. For the purpose of reporting standardised findings for research, two independent radiologists reported the MRI findings for all trial participants. The radiologists interpreted the report according to the MRI findings only.

Tuberculosis screening and biological agent counselling

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

Second physiotherapy assessment

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

Registration

Once the first consent had been obtained, participants' details were recorded on a database in the trial centre and each participant was assigned a unique participant identification number. Anonymised details labelled with the unique participant identification number were transferred to a separate database in the trials unit, which was used for recording all of the trial data. All databases were password protected. The participant consent forms were stored in a locked filing cabinet in each treatment site. Participants' GPs were informed in writing about their participation in the trial.

Randomisation

After completion of the second consent form and once baseline outcome measures had been collected, participants were individually randomised. Randomisation to the Subcutaneous Injection of Adalimumab Trial compared with Control (SCIATiC) was achieved by secure web access to the remote randomisation system at the trials unit. This system was maintained and monitored independently of the trial statistician and any trial staff who needed to remain blind to the treatment allocation. In order to protect against subversion, while ensuring that the trial maintained good balance to the allocation ratio of 1 : 1 both within each stratification variable and across the trial, the randomisation was performed using a dynamic adaptive randomisation algorithm.[36] Participants were stratified by (1) treatment centre and (2) presence of neurological signs (motor weakness or sensory loss). The research physiotherapist who obtained informed consent requested the randomisation code from the web-based randomisation system, the result of which was e-mailed to the pharmacy and the rheumatology nurse, but not the research physiotherapist. The dispensing pharmacist logged and dispensed the appropriate injection in line with Medicines and Healthcare products Regulatory Agency (MHRA) guidelines. The injection was given on the day of randomisation; if this was not possible, a further appointment was arranged by the research physiotherapist so that the treatment could be given within 3 days from randomisation.

Withdrawal of participants

Withdrawal from the trial did not affect participants' medical care, something that was emphasised in the participant information sheet. Failure to complete any one follow-up assessment did not constitute formal

withdrawal from the trial, and, unless participants requested complete withdrawal of their data, data were used to impute values for the analysis. The imputation of missing values ensured that the data set was utilised to its full power. The full imputation details were prespecified as part of the statistical analysis plan.

Expected duration of trial

We planned to recruit participants over a 20-month period and to follow them up for 12 months.

Subcutaneous injections

All participants were randomised to receive two doses of subcutaneous injection, 2 weeks apart, into the posterior thigh. The intervention group received 80 mg of adalimumab followed by 40 mg,[18] in order to achieve a therapeutic dose of adalimumab for a period of 4 weeks. The control group received an equivalent volume of 0.9% sodium chloride.

Injection process

The injections were prescribed by a consultant rheumatologist and administered by a rheumatology nurse experienced in the administration of these injections. The first injection was given on the same day as randomisation; if this was not possible, a further appointment was arranged by the research physiotherapist so that the treatment could be given within 3 days of randomisation. It was not possible to make the adalimumab and placebo syringes indistinguishable in appearance, nor was it possible to blind the pharmacy or the rheumatology nurse who administered the injections. Blinding of participants and the other clinicians was maintained using the following strategies. The rheumatologist wrote a prescription for 'SCIATiC trial injection' and was kept blind to treatment allocation. The research physiotherapist who obtained informed consent requested the randomisation code from a web-based randomisation system. The randomisation code was not sent to this physiotherapist, but was e-mailed to the pharmacy and the rheumatology nurse. The rheumatology nurse collected the injection from the pharmacy, which was transported in an undistinguishable box containing the adalimumab inside its original packaging or the 0.9% sodium chloride-containing ampoules. Communication between the participant and rheumatology nurse concerning the injection was kept to a minimum, and the rheumatology nurse administered the injections into the participant's posterior thigh. The research physiotherapist was not present and did not communicate with the rheumatology nurse about the injection. In addition, in order to provide reassurance that other clinicians were not present, a log was kept of all people present in the room when each injection was administered. All research staff received full training on the blinding procedures. In order to assess whether or not blinding had been maintained, the participants were asked to complete a five-point Likert scale that asked if the participant considered the treatment 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.

Concurrent physiotherapy

Physiotherapy is usually considered normal practice for those participants who fail to improve with GP care alone. In this trial we aimed to investigate the clinical 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 relieve pain.[37] There was also evidence that exercise-based physiotherapy treatment added to GP care was beneficial.[38] Regimes including strengthening exercises of the lumbar and pelvic muscles also show some promise in terms of improvements in this group of participants. In this trial, both groups received a concurrent course of physiotherapy intervention that could be described as 'best conservative care'. It was delivered in local physiotherapy departments by 'treating' physiotherapists and not by the 'research' physiotherapists who were carrying out the assessments of eligibility and randomisation. The physiotherapy intervention consisted of a package of directional preference (McKenzie), strengthening exercises or other exercises,[37,38] and manipulative techniques that had been determined by consensus using a panel of extended scope physiotherapists. Treatments were intended to 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; and encouragement of appropriate, gradual return to full function, including work when applicable. The first session was expected to last approximately 45 minutes, with subsequent sessions lasting 30 minutes each. The therapy sessions were to be provided over a period of 12 weeks. The number of sessions provided would be determined by participant and therapist preference, and also response to treatment. We captured and described these aspects of physiotherapy treatment as part of the trial. The physiotherapy treatment started at the same time as the injection intervention in both arms of the trial. Participants were discouraged from receiving any other NHS-based co-intervention until this physiotherapy treatment had finished.

Clinical management of persistent symptoms

The protocol was designed such that, once the participants had completed their course of physiotherapy, and symptoms had settled or were improving, then no further intervention would be organised. They were to be discharged to the care of their GP and followed up by the research team. If troublesome symptoms persisted, then further treatment could be planned, as appropriate, by referral to musculoskeletal interface clinics or secondary care specialists according to local arrangement in each of the centres. The plans for further treatment were at the discretion of the treating clinicians and could include epidural corticosteroid injections or referral for disc surgery. The full result of MRI was to be made available if a spinal surgery referral was contemplated. All additional treatments were recorded in detail in a case report form.

Internal pilot trial

The pilot built on previous research in this participant group undertaken by team members,[20,21,30,39] which had already provided information on trial administration, the characteristics of sciatica participants and the effects of biological treatments from previous studies. The internal pilot was designed to rehearse the procedures and logistics to be undertaken in the main trial. It was designed to assess the feasibility of the arrangements for delivering the interventions, recruitment rate and initial retention rate. The internal pilot would be based on the first 50 participants recruited into the trial. We planned to start recruitment in two centres (North Wales and London) and then to roll out recruitment in the other three centres over the following 3 months. We expected the recruitment rate to build up over the first 3 months to the target rate of four participants per collaborating centre per month. We anticipated that this would take 7 months. The indicative stopping criteria at the end of this internal pilot were recruitment, which failed to reach 80% of the planned recruitment rate target, dropouts up until the 6-week postal questionnaire assessment exceeding 20% or more than one centre failing to commence recruiting. Any procedural changes identified in the pilot would be implemented across all trial sites subject to ethics approval of the appropriate major amendment. Data from participants in the internal pilot would be automatically rolled into the main trial data unless the Trial Management Group (TMG) believed that data were incompatible with the remaining data. No interim analysis at the primary end point (1 year) was proposed and,

therefore, this internal pilot would not affect the overall power of the trial. Wittes and Brittain's[40] method would be used for sample size recalculation if required.

Primary outcome

The primary clinical outcome was back pain-specific disability measured using the ODI[33] at 12 months. The primary economic outcome was the incremental cost per QALY gained, estimated by administering the EQ-5D-5L[34] at each follow-up visit.

Outcome measures

Condition-specific outcomes

- Back pain-specific disability using the ODI.[33]
  The ODI 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 items 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 that 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 scoring 5 and indicating the most severe disability. The index is converted to a percentage score from 0 to 100. Zero is equated with no disability and 100 with maximum disability. It was 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 score was used as the baseline measurement. It would also be measured at follow-up after 6 weeks, and at 6 and 12 months.
- Leg pain-related functional disability using the leg pain version of the Roland–Morris Disability Questionnaire (RMDQ).[41,42]
  The RMDQ is a measure of disability in which 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 place a tick against appropriate questions based on how they feel each sentence describes them on that day. If the sentence does not describe their symptoms that day, participants are asked to leave the space next to the sentence blank. The RMDQ is scored by adding up the number of items checked by the participant. The score can therefore vary from 0 to 24 points. If a participant indicates in any way that an item is not applicable to them, the item is scored 'no' (i.e. the denominator remains 24). It was measured at baseline and at 6 weeks' and 6 and 12 months' follow-up.
- Leg pain interference using the Sciatica Bothersomeness Index.[43]
  This is an index based on participants reporting symptoms that reflected the trouble the participant is going through with his/her sciatica symptoms. The index included self-reported ratings of symptom intensity of leg pain; numbness or tingling in the leg, foot or groin; weakness in the leg/foot; or 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 was measured at baseline and at 6 weeks' and 6 and 12 months' follow-up.
- Pain location using a pain manikin.[44]
  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 was used at baseline, 6 weeks', and 6 and 12 months' follow-up.

Generic outcomes

- Health utility using the EQ-5D-5L.[34]
  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 was used at baseline and at 6 weeks' and 6 and 12 months' follow-up. It allowed the calculation of QALYs, using the area under the curve method, which would 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 was measured at 6 weeks' and at 6 and 12 months' follow-up.

Psychological outcomes

- Anxiety and depression using the Hospital Anxiety and Depression Scale.[45]
  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 seven items for depression. Participants are asked whether they experience the symptom definitely, sometimes, not much or not at all. The Hospital Anxiety and Depression Scale was designed for use in the hospital setting but has been used successfully with the general population. It was used at baseline and at 6 weeks' and 6 and 12 months' follow-up.

Use of health-care and social-care services

- Resource Use Questionnaire.[46,47]
  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 was administered at baseline and at 6 weeks' and 6 and 12 months' follow-up.

Employment

- Questions on employment status, work absence, sick certification and self-certification.
  These were used at baseline and at 6 weeks' and 6 and 12 months' follow-up.

Process measures (potential predictors and mediators of outcome)

Risk of persistent disabling pain was assessed using the following tools:

- STarT Back Screening Tool.[48]
  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 was measured at baseline only.
- Pain trajectory based on a single question.[49]
  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: < 3 months, 3–6 months, 7–12 months, 1–2 years, 3–5 years, 6–10 years and > 10 years. This shows that recalled duration of pain is a predictor of outcome in patients with low back pain, independent of baseline severity and psychological status.
- Pain Self-Efficacy Questionnaire (PSEQ).[50]
  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 and work, as well as coping with pain without medication. It was used at baseline and at 6 weeks' and 6 and 12 months' follow-up.

- Fear of movement using the Tampa Scale of Kinesiophobia.[51]
  The Tampa Scale of Kinesiophobia 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/reinjury. It was used at baseline and at 6 weeks' and 6 and 12 months' follow-up.

Follow-up

The questionnaires followed best practice in their design, to maximise response rate. The baseline questionnaire was administered by the research physiotherapists and completed by the participant. We planned to send follow-up postal questionnaires at 6 weeks, and at 6 and 12 months. Non-responders were to be sent an additional copy of the questionnaire. Persistent non-responders were to be contacted by telephone in order to collect a minimum data set. We planned to contact all participants by telephone 2 weeks after the 12-month questionnaire was sent. This would allow us to collect a minimum data set from non-responders, and to conduct a a brief semistructured interview with all participants asking about their overall experience of the trial and subsequent follow-up treatment. Blinding to treatment allocation would be maintained during these telephone interviews. Once again, in order to assess if blinding had been maintained, participants would be asked to complete a five-point Likert scale about which treatment group they believed that they were in.

Assessment of safety

As part of site initiation, training included an overview of possible side effects/potential adverse reactions associated with adalimumab.

Recording adverse events and adverse reactions

All trial staff and clinicians in contact with trial participants were responsible for noting adverse events reported by participants and making them known to appropriate medical staff. Trial participants were encouraged from the outset to contact the research team at the time that an event occurred. Participants were given a leaflet or card containing a contact address and telephone number. All adverse events, including non-serious adverse events, were recorded in the participant's medical records and on their case report form. All adverse events were reported up to 1 month after the conclusion of the physiotherapy intervention. Adverse events included:

- 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 worsened following administration of the trial treatment.

The following were not included as adverse events:

- medical or surgical procedures in which the condition that led to the procedure was the adverse event
- pre-existing disease or conditions present before treatment that did not worsen
- overdose of medication without signs or symptoms.

Recording serious adverse events and serious adverse reactions

The definition of a serious adverse event was any medical event that:

- resulted in death
- was 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 that might have caused death had it been more severe in nature)
- required hospitalisation, or prolongation of existing hospitalisation
- resulted in persistent/significant disability or incapacity
- was a congenital abnormality or birth defect.

Serious adverse events also included were other important medical events that, based on appropriate medical judgement, may have jeopardised the participant and may have required medical or surgical intervention.

Any serious adverse events and serious adverse reactions were recorded in the 'Investigator Site File' and the 'Trial Master File'.

Statistics

Sample size

From the WMD in our previous meta-analysis,[21] we found a relative improvement of 8 points in the ODI at 6 months' follow-up in the group receiving biological agents compared with placebo, with a standard deviation of 16 points, 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 was needed. We aimed for a 90% return rate of the final questionnaires but, for a more conservative retention rate of 80%, 332 participants needed to be recruited. If, as is likely, there was any correlation between the baseline and outcome measure, the size of effect detectable would be smaller (or the power to detect a 0.4 effect enhanced).

Recruitment rate

Calculations of recruitment rates for SCIATiC 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 [Assessment and Treatment of Leg pain Associated with the Spine (ATLAS) trial cohort].[39] The ATLAS study recruited 609 patients from 17 general medical practices (approximate total adult population of 90,200) over 24 months. Analysis of the recruitment data shows that 219 (36%) participants in this cohort had sciatica with pain in one leg only (with > 80% diagnostic confidence,) with a RMDQ score of > 7 points (equivalent to an ODI score of ≥ 30 points). On average, per month, 86 potential participants were identified by GPs and referred to the ATLAS study, 54 attended the physiotherapy-led research clinic and 25 gave consent and were eligible for the study, nine of whom had a clinical diagnosis of sciatica (spinal nerve root pain) satisfying the conditions described in *Inclusion criteria* and *Exclusion criteria* in terms of disability score and diagnostic confidence. Based on these figures and taking into account that in the ATLAS study 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 was four participants per collaborating centre per month, with centres covering similar sized populations. For SCIATiC, North Wales, Keele and Cardiff aimed to recruit from GP practices with a combined registered population of at least 100,000 per centre.

Data analysis

All data were anonymised and coded so that data collection and statistical analysis were performed blind to treatment allocation. The code would be broken only after the primary analysis had been completed. The analysis would be performed on a 'treatment as allocated' principle to ensure protection against

unintended bias. The data would be fully imputed using a multiple imputation by chain equations approach[52] in line with a predefined statistical analysis plan to minimise data loss as a result of missing values or time points. Participants who needed to be referred for disc surgery would be labelled as 'treatment failures' and their last test results prior to surgery would be carried forward in the analysis. Sensitivity analyses (best case/worst case) would be performed to assess the influence of different imputation assumptions. All trial reporting was Consolidated Standards of Reporting Trials[53] compliant.

Primary analysis

The main outcome variable was the ODI measured at 12 months. A linear mixed-model approach for repeated measures would be used to assess the effects of time and group, while time × group effects would further describe and explain the overall finding (the interaction term would assess whether or not the effect of the intervention was the same at each time point). The use of a linear mixed model for analysis should take care of missing data; however, if imputation was required, then the multiple imputation by chain equations approach described would have been used. This model would be fully defined in the statistical analysis plan prior to all analyses. This statistical analysis plan would be approved by all lead investigators and site principal investigators (PIs), and available for comment by the independent committees prior to sign-off.

Secondary analysis

Secondary continuous outcome variables would be assessed in a similar way to the primary outcome variable, with the exception of time to referral for surgery, which would 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 would be explored using logistic regression. These analyses would be repeated using prespecified participant subgroups (including the presence of neurological deficit on entry to the trial and MRI findings). Subgroups would be defined within the statistical analysis plan prior to the analyses beginning.

Economic analysis

The health economic analysis would adopt the perspective of the NHS and Personal Social Services, with the inclusion of indirect costs (e.g. time off work) as a secondary analysis. Costs included those of treatment, tests, procedures and investigations, contact with primary and secondary care services and personal social services. Resource use would be obtained from participants' self-reporting of resource use, captured by questionnaire administration.[46,47] Unit cost data would be obtained from standard sources[54] and other resources such as the *British National Formulary*.[32] The primary economic outcomes would be the incremental cost per QALY gained, estimated by administering the EQ-5D-5L at each follow-up point. The number of QALYs gained by each participant would be calculated as the area under the curve, using the trapezoidal rule, applying the UK tariffs and corrected for baseline utility score. When appropriate, missing resource use or health outcome data would be imputed.[55] Non-parametric bootstrapped 95% CIs would be estimated (10,000 replicates). Stratified cost-effectiveness analyses would be conducted on important, prespecified participant subgroups. Total costs would be combined with QALYs to calculate the incremental cost–utility ratio of the package of adalimumab plus physiotherapy compared with a 0.9% sodium chloride injection plus physiotherapy. Estimates of incremental cost–utility ratios would be compared with the £20,000–30,000 per QALY threshold of cost-effectiveness, and a range of one-way sensitivity analyses would be conducted to assess the robustness of the analysis. Multivariate sensitivity analyses would be applied when interaction effects were suspected. The joint uncertainty in costs and benefits would be considered through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves.[56]

Trial management

Trial Management Group

Individuals responsible for the day-to-day running of the trial were included in a TMG, which included the chief investigator, lead investigators, PIs, trial manager, statistician, health economist, site co-ordinators, research staff, data manager and collaborating clinicians, as necessary. The TMG's role was to monitor all aspects of the trial's set-up, conduct and progress. The group ensured that the protocol was adhered to, and would take appropriate action to safeguard participants and ensure the overall quality of the trial. The TMG reported to the Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC), and met every 1–2 months.

Trial Steering Committee

A TSC was set up to oversee the running of the trial on behalf of the sponsor and funder, and had the overall responsibility for the continuation or termination of the trial. The TSC had an independent chairperson and a majority of independent members and included a patient representative. The role of the TSC was to ensure that the trial was conducted in accordance with the principles of 'good clinical practice' and the relevant regulations, and it provided advice on all aspects of the trial. The trial protocol and any subsequent amendments were agreed by the TSC. The TSC reported to the TMG, the sponsor and the funder and it met every 6 months.

Data Monitoring and Ethics Committee

A DMEC monitored the progress of the trial and reviewed all adverse events. The DMEC would have reviewed results from the internal pilot trial and advised the TSC as needed. It met every 6 months.

Reporting

The TMG reported to the DMEC and TSC. The DMEC reported to the TSC and the TSC reported to the TMG, the sponsor and the funder. Safety reports were submitted every 6 months to the Research Ethics Committee (REC), the sponsor and the funder. Development update safety reports were submitted to the MHRA.

Direct access to source data and documents

Source data were the hospital-written and NHS electronic medical records. Access to these data was through the participant's clinicians, physiotherapist and research nurse. Trial-related monitoring, audits, REC reviews and regulatory compliance inspections were permitted, allowing access to data and documents when required.

Quality assurance

This trial was conducted in line with the trial protocol and followed the principles of good clinical practice outlined by the *International Committee of Harmonisation Good Clinical Practice E6 (R1) Current Step 4 Version*[57] and complied with the European Union directive 2001/20/EC.[58]

A monitoring plan was developed based on a trial risk assessment, which provided details of day-to-day quality control, audits, etc., and was delegated to members of the trial team to ensure that collected data adhered to the requirements of the protocol; only authorised persons completed case report forms; the potential for missing data was minimised; data were valid through validation checks (e.g. range and consistency checks); and recruitment rates, withdrawals and losses to follow-up were reviewed overall and by hospital site.

Data handling

The sources of data for the trial were 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 6 weeks' and at 6 and 12 months' follow-up entered into the MACRO system (version 4; InferMed, London, UK); and 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, would be recorded electronically on the computers. Each centre would input data into the MACRO data management program, which is a web-based system allowing controlled access to data by all centres and allows a full audit trail.

Trial sponsor

Bangor University (reference number 12/201/02; contact Dr Huw Roberts).

Ethics approval

Wales REC-3 granted approval on 27 May 2015 (15/WA/105). Clinical trial authorisation was approved from the MHRA on 15 April 2015 (21996/0002/001-0001).

Chapter 3 Results

Trial progress

Funding for the trial was approved by the HTA programme on 11 August 2014; the intention at that time was for the trial to open in January 2015 and close in June 2018. It had been planned that all the trial documentation for the regulatory approval for the trial would be completed between July 2014 and December 2014 so that regulatory approval could be obtained by January 2015.

Five collaborating sites planned to participate in the trial – North Wales, Cardiff, London, Keele and Nottingham – with training at the five sites taking place between February 2015 and April 2015. The initial plan was that the trial would be set up and recruiting participants at North Wales and London by April 2015, with the other sites opening to recruitment in June to October 2015. The trial documentation for the regulatory approval was not in place until December 2014. Regulatory approval was obtained from the MHRA on 15 April 2015 and from the REC on 27 May 2015. During this time the three English sites submitted requests for excess treatment costs (ETCs) to the NHS England for Clinical Commissioning Groups, ETCs for the two Welsh sites were agreed, and contracts were sent to both lead and collaborating sites from the sponsor, Bangor University. There were delays and unforeseen complexities in obtaining the ETCs for the English sites. Contracts also proved an issue and caused major delays because of difficulties with the delegation of the roles and responsibilities and what was required within the different contracts between university and university, and university and NHS sites. One of the sites withdrew from the trial in February 2016 because of concerns about the dosage of the biologic used and its patient population, which was higher than the standard dose used for patients with rheumatoid arthritis but similar to dosage in other conditions. This withdrawal led to a risk review for the other sites, which felt that, as no new data were available, the risk of infection for participants was acceptable, and they all agreed to continue participating in the trial.

The trial opened to recruitment on 8 December 2015 at North Wales and Nottingham, with Keele opening to recruitment on 11 August 2016. At the time of trial closure, contractual discussions were still ongoing between Bangor University, Cardiff University and Cardiff and Vale University Health Board.

During this time all sites dealt with a number of challenges. In North Wales, a research physiotherapist was seconded to the trial in September 2015 but, because of a shortage of physiotherapists in the department, was required by the health board to return to their previous employment and then left the post in February 2016 for personal reasons. As a result of physiotherapy staffing shortages within Betsi Cadwaladr University Health Board (BCUHB), the site was unable to employ a replacement research physiotherapist for the required research physiotherapist time. Participants were identified and recruited via the musculoskeletal clinic and physiotherapy clinics. The PI at the site contacted fellow consultants throughout the health board to ensure that all potential participants were identified. Only three participants were recruited at this site between March and July 2016.

Nottingham had intended to recruit its participants for the trial from the Sherwood Forest Hospitals NHS Foundation Trust Back Pain Unit diagnostics clinics only, based on pre-study clinic data. During the first 3 months after the start of recruitment at that site, no eligible participants were identified. The site PI extended screening to include orthopaedic clinics in addition to back pain unit clinics, but without any significant increase in recruitment. The PI at this site investigated whether or not there had been a change in referral pathways for people with sciatica in the region that might have affected referrals into these clinics. The PI confirmed, in February 2016, that this had been the case. GPs had been given direct access to MRI scans for sciatica, and were requesting and reviewing the results of MRI before requesting opinion or treatment from the back pain service. As well as introducing delay to referrals, the local GPs were

tending to refer those with sciatica and a congruent disc prolapse on MRI to an alternative spinal surgical unit (e.g. Nottingham University Hospitals NHS Trust). A potential participant referred to the PI had already received MRI, which made them ineligible. Trial progress was an agenda item at the TMG. Owing to changes in pathways at Sherwood Forest Hospitals NHS Foundation Trust Back Pain Unit, it was agreed by the TMG that the protocol should be amended to include participants who had already undergone MRI. This was approved by the REC on 15 April 2016 and by the MHRA on 27 May 2016. During this time, Sherwood Forest Hospitals NHS Foundation Trust had also been in discussions with local primary care colleagues to arrange identification of potentially eligible participants from local GP practices through database searches or opportunistic referral. This was agreed and implemented in June 2016. Sherwood Forest Hospitals NHS Foundation Trust recruited five participants to the trial between February and September 2016.

During this period, Keele had obtained agreements for its ETCs and contract negotiations were finalised between Bangor University and Keele University, and between Bangor University, Keele University and Royal Wolverhampton NHS Trust, and also between Bangor University, Keele University and Staffordshire and Stoke-on-Trent Partnership Trust. The Royal Wolverhampton NHS Trust was opened to recruitment on 11 August 2016; one potential participant was identified prior to the trial closure on 20 September 2016. Randomisation of this participant was not permitted as a result of trial closure on 26 September 2016.

The TSC met on 11 January 2016. The problems with recruitment were discussed at the meeting, and the members were very sympathetic to the trial team's frustration of the poor recruitment to the study. The TSC recommended the following steps if the funders allowed the trial to continue:

1. optimise recruitment for the two sites that were open
2. work harder to reduce bottlenecks (e.g. more MRI slots in North Wales)
3. increase the number of general practices searching for potential participants
4. approach the musculoskeletal triage clinics to join the study as sites
5. inform Keele and Cardiff at the next management group meeting that if they were not about to start recruiting then they would no longer be part of the trial
6. contact other possible sites that would be able to recruit to the study within the next 6 months.

The chief investigator contacted four sites one each in north, south and mid-Wales, and also the Royal Free Hospital in London.

Although the additional North Wales site was eager to participate and there was sufficient staff, there was a lack of clinical space to accommodate the trial within the rheumatology department. The rheumatology consultant submitted a case to the hospital managers with plans to increase the space available to carry out clinical trials. Unfortunately, this request was turned down because of competing demands on clinical space in the hospital, so it was not possible for the rheumatology department to be involved with SCIATiC and other clinical trials.

The hospital site in south Wales had expressed interest in participating in the trial in April 2016, and the site was arranging to accommodate the trial when we had to notify them that the trial was terminating early.

The hospital site in mid-Wales had also expressed interest in participating and had notified us on 17 August 2016 that its physiotherapy team had agreed to accommodate the trial. Unfortunately, we informed the site on 18 August 2016 about the discussions that we had with the funders and the expected termination of the trial.

The Royal Free Hospital had been discussing increasing their portfolio of clinical trials within the physiotherapy department and in April 2016 had expressed interest in participating. Unfortunately, it later informed us that it was doubtful if it would receive funding for the intervention arm of the trial. The hospital also felt that it would have difficulty recruiting participants with a symptom duration of

< 6 months. In addition, its rheumatology department did not have spare capacity as it was already busy with existing research activities.

Owing to concerns with the slow recruitment, the chief investigator and Bangor trial team met with the funders on 28 January 2016, who informed the trial team that they should:

- finalise existing contracts immediately
- open sites that had not yet opened within the month
- start recruiting from all sites
- complete recruitment to the internal pilot of 50 participants by June 2016.

Another meeting with the funders was held on 16 August 2016. At the meeting the funders requested that the project team should submit closedown proposals as soon as possible and, ideally, by no later than 31 August 2016. Two different scenarios were proposed:

1. an immediate closedown of recruitment with submission of the project report by the end of December 2016
2. closure of recruitment in 6 months, until which time the study team should seek to establish the most effective recruitment routes for any future study, with submission of the project report by the end of June 2017.

From 16 August to 26 September 2016 only one participant was randomised to the trial by the Sherwood Forest Hospitals NHS Foundation Trust site. This information was relayed back to the funder, and on 26 September 2016 the chief investigator confirmed that the funders had asked for the trial to be closed immediately and the project report to be completed by the end of December 2016.

Trial timetable

The trial timetable is outline in *Table 2*.

Trial recruitment

Recruitment data for the trial are presented in *Figure 3* and reasons for withdrawal or exclusion in *Table 3*. Sherwood Forest Hospitals NHS Foundation Trust and BCUHB recruited from December 2015 to September 2016. The Royal Wolverhampton NHS Trust recruited from August 2016 to September 2016. During this time, eight participants were randomised. No adverse events or adverse reactions were recorded for any of the participants.

Contracting delays

Site contracts were a major issue. Initial contract templates were drafted in November 2014 but could not proceed further until the contract and finances were agreed with the funder, and the funder did not provide these until February 2015. Draft subcontracts were sent to the relevant parties from the Bangor University contracts department on 31 March 2015.

Betsi Cadwaladr University Health Board: Peter Maddison Rheumatology Centre, Llandudno Hospital

The subcontract was signed on 8 April 2015; the time taken was 9 days.

TABLE 2 Trial timetable

Event	Date of completion	
	Expected	Actual
Finalised protocol and trial documentation	July–December 2014	January 2015
Ethics and NHS R&D permission/MHRA approvals	September 2014–February 2015	MHRA – April 2015
		REC – May 2015
		BCUHB R&D approval – July 2015
		SFHT R&D approval – November 2015
		RWT R&D approval – August 2016
Contracts signed and completed	January–March 2015	BCUHB – April 2015
		SFHT – October 2015
		Bart's Health NHS Trust – September 2015
		RWT – July 2016
Staff training and site initiation	March–May 2015 and November–December 2015	June 2015, July 2015, September 2015 and November 2015
Set up of centres to recruitment	February–March 2015	BCUHB – December 2015
		SFHT – December 2015
		RWT – August 2016
Identification of potential participants	February 2015–August 2016	December 2015
Telephone screening	March 2015–September 2016	December 2015
Physiotherapy clinical assessment	April 2015–October 2016	December 2015

R&D, research and development; RWT, Royal Wolverhampton NHS Trust; SFHT, Sherwood Forest Hospitals NHS Foundation Trust.

Nottingham University/Sherwood Forest Hospitals NHS Foundation Trust: Rheumatology Department, King's Mill Hospital

The subcontract with Sherwood Forest Hospitals NHS Foundation Trust was signed on 20 October 2015; the time taken was 197 days. The collaborative agreement with Nottingham University was signed on 7 July 2016; the time taken was 378 days.

Initial agreement was sent to Sherwood Forest Hospitals NHS Foundation Trust and Nottingham University on 31 March 2015. A draft academic agreement was sent to Nottingham University by Bangor University on 25 June 2015, along with a reminder regarding the NHS contract, and a response was received from the PI on 16 July 2015. Nottingham queried their costings on 3 August 2015, and costings were confirmed by Bangor University on 4 May 2016; the collaborative agreement was signed on 7 July 2016. Bangor University received an update from the Sherwood Forest Hospitals NHS Foundation Trust site on 15 September 2015 stating that they were awaiting an internal response, and the NHS trust contract was signed on 20 October 2015.

Queen Mary University of London/Bart's Health NHS Trust: The Royal London Hospital

The collaborative agreement with Queen Mary University of London was signed on 24 July 2015; the time taken 115 days. The subcontract with Bart's Health NHS Trust was signed on 14 August 2015; the time taken was 131 days.

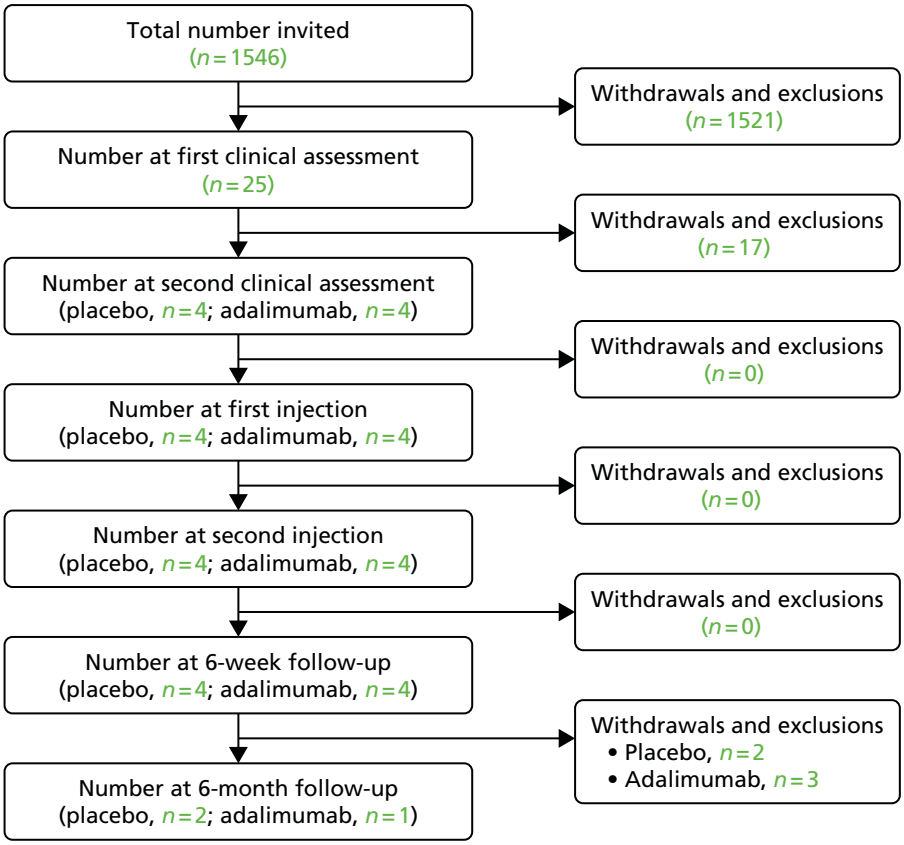

FIGURE 3 Participant flow diagram for Sherwood Forest Hospitals NHS Foundation Trust, BCUHB and the Royal Wolverhampton NHS Trust.

An initial agreement was sent to Bart's Health NHS Trust and Queen Mary University of London on 31 March 2015. Bangor University received a response from the site on 21 July 2015 stating that the site agreed with the terms of the contract. On 24 July 2015, the site contacted Bangor University to say that, as the template had been approved by the funder, they could move to signature. The collaborative agreement was signed on 24 July 2015 and the subcontract with the NHS trust was signed on 14 August 2015.

Keele University/Royal Wolverhampton NHS Trust: Cannock Chase Hospital and New Cross Hospital

The collaborative agreement with Keele University was signed on 2 June 2016; the time taken was 427 days. The subcontract with the Royal Wolverhampton NHS Trust was signed on 7 July 2016; the time taken was 459 days.

The initial agreement was sent to Keele University on 31 March 2015, with service-level agreements to be sent to the NHS sites by Keele University. Initial feedback was received from Keele University in May 2015 with a response to these from Bangor University in June 2015. At a meeting on 22 July 2015 in Keele, contracts were discussed with the trial manager and the research team at Keele University, considering either (1) a tripartite contract between Bangor University, Keele University and the two sites at Royal Wolverhampton Hospitals NHS Trust (Cannock Hospital and New Cross Hospital) or (2) a contract from the sponsor directly to the NHS sites. During further discussions between the contract departments of Bangor and Keele universities, it was agreed that the following subcontracts would be used: Bangor University and Keele University, and Bangor University and Royal Wolverhampton Hospitals NHS Trust. Another contract was also required between Bangor University and Staffordshire and Stoke-on-Trent Partnership Trust, as patients in the trial would be treated by physiotherapists in Royal Wolverhampton Hospitals or from Staffordshire and Stoke-on-Trent Partnership Trust. The collaborative agreement was signed on 2 June 2016. Further discussions concerning the delegated duties and wording of the contract to clarify the role of the NHS sites meant that the subcontract was not agreed and signed until 7 July 2016.

TABLE 3 Reasons for withdrawal and exclusion for patients in Sherwood Forest Hospitals NHS Foundation Trust, BCUHB and the Royal Wolverhampton NHS Trust

Reason for withdrawal and exclusion	*n*
From invitation to first clinical assessment	1520
Did not confirm interest	963
Symptoms persisting for > 6 months	173
Previous episode of sciatica in the last 6 months	2
Contraindications to MRI	6
Serious spinal pathology	4
Incidental serious pathology identified by MRI	1
Widespread pain throughout body	25
Previous use of biological agents targeting TNF-α	1
Previous lumbar spinal surgery	16
Contraindications to adalimumab	1
Pregnant or breastfeeding	1
Unable to communicate in English or Welsh	3
Mental health problems	3
No sciatica	210
Previous surgery	11
No leg pain	20
Complicated symptoms	18
Pain in both legs	7
Expressed interest but delay in telephone screening attributable to site staffing issues means no longer meet criteria for inclusion (e.g. no longer in pain or have recently breached the > 22-week exclusion window since replying)	6
No response or no longer interested	23
Symptoms resolved/improved	10
Current leg pain worse than or as bad as back pain	3
Trial closed early to recruitment	14
From first to second clinical assessment	17
Over time limit for second clinical assessment	1
Study closure	5
Mild symptoms – discharged to GP care	7
TB screening failed	1
Participant revealed long-term history of widespread pain at screening – particularly in shoulders	1
No positive neurological test	1
Patient did not attend appointment and could not be contacted	1
From 6-week to 6-month follow-up	4
Study closure	4

Cardiff University/Cardiff and Vale University Health Board

The subcontract was still being discussed at the termination of the trial in September 2016, 18 months after the initial draft had been sent. There were several unresolved issues. Cardiff University decided that it wanted a tripartite subcontract between Bangor University, Cardiff University and Cardiff and Vale University Health Board. However, after agreeing to this tripartite agreement, it decided not to sign, as it wanted to use the Brunswick model agreement.[59] Initially MRI was to be undertaken by Cardiff University, but because this was allocated to the university, rather than the health board, only 80% of the cost would be reimbursed, and who should pay for this underspend was left unresolved. This delay in signing the contract also meant that the research physiotherapist seconded to the post was not able to sign her secondment contract and had to return to her original post. A teleconference took place on 21 January 2016 to resolve the outstanding issues. As a result, an updated subcontract was sent with an updated work schedule, but remained unsigned.

The funder also requested oversight of all the subcontracts before they were signed. Delays with the subcontracts led to delays with recruitment and retention of staff at the trial sites. It also meant that a great deal of trial management time that could have been spent on finding solutions to the slow recruitment was instead expended on contracting issues.

Withdrawal of site

Eight months after initiation, Bart's London, one of the larger sites, revisited the risk assessment of the trial and felt the participant population in its area meant that the 80-mg initial dose would confer a risk of infection that was higher than acceptable. Bart's London therefore decided to withdraw its participation in the trial. This withdrawal led to a risk review for the other sites, all of which felt that, as there were no new available data, the risk of infection for their participants was acceptable and agreed to continue participating in the trial.

Recruiting research physiotherapists at sites

It took longer than anticipated to obtain research and development (R&D) approval and set up the site, and this led to delays in recruiting research physiotherapists. Just after the BCUHB site had opened to recruitment, the research physiotherapist, who had been seconded to the post from the NHS physiotherapy department, was required to return to her clinical duties because of staff shortages. This had a negative effect on the trial, as it halved the physiotherapist time available for screening and recruiting participants to the study at that site. The chief investigator complained to the department that this removal was jeopardising the trial, and it was agreed that it would only be for 6 weeks until a locum could be employed. Unfortunately, the same research physiotherapist went on long-term sick leave and was advised by the health board's occupational health department not to return to the post of research physiotherapist. This led to delays in recruiting participants into the trial and resulted in the loss of some potential participants who had expressed an interest, as there was no physiotherapist to screen and recruit them.

This resulted in a change of protocol whereby a medically qualified member of staff could be used to screen potential participants if a research physiotherapist was unavailable. In the interim, Health and Care Research Wales nurses assisted with the screening of potential participants and another physiotherapist was assigned to assist with the recruitment of participants to work on the trial for one session per week for 5 months. A rheumatology registrar was trained in the trial procedures, but was only available to recruit potential participants for 1 month after regulatory approvals were complete.

Slow recruitment at open trial sites

Recruitment was slower than anticipated in both BCUHB and Sherwood Forest Hospitals NHS Foundation Trust, which were opened to recruitment on 8 December 2015. Royal Wolverhampton NHS Trust opened on 11 August 2016; the trial was closed on 26 September 2016. No participants could be recruited by Royal Wolverhampton NHS Trust in this time.

In BCUHB, 16 GP practices identified eligible patients presenting at the practice by database searches or opportunistic referral. An application was made to increase the funding for NHS support costs to cover the costs of 30 practices, but this was not in place before the trial closed. Musculoskeletal clinics and physiotherapy departments also searched for eligible patients presenting to their clinics.

At Sherwood Forest Hospitals NHS Foundation Trust, patients referred to the musculoskeletal service at the rheumatology clinics were screened for eligibility. It was noted by the PI at this site that the number of sciatica patients referred to the clinics had fallen as a result of a change in the referral pathway commissioned by the local commissioning group. At this site it was then decided to invite GP practices to identify eligible patients presenting at the practice, by database search or opportunistic referral. Database searches commenced at 12 practices in June 2016. A total of 756 potential participants were identified, 11 were invited to first clinical assessment screening and five participants provided consent to participation before the trial was terminated.

At Royal Wolverhampton NHS Trust, R&D approval was agreed and contracts signed on 7 July 2016, just before the trial was terminated. One patient was screened but was not invited to provide consent to participation prior to trial closure.

Excess treatment costs

Applications for ETCs were agreed by the Welsh Government by the two Welsh sites, but agreement for the three English sites was more problematic. On 4 February 2014, the trial chief investigator asked all participating sites to submit an application for ETCs. This was submitted by Sherwood Forest Hospitals NHS Foundation Trust in June 2014, and the ETCs were approved on 11 March 2015. Discussion had also taken place in Wolverhampton and an application submitted, but ETCs had been declined because of insufficient funds. This site subsequently explored other potential sources of funding (e.g. from primary and secondary care, or the pharmaceutical company Abbott UK, if they could provide a discounted or free drug). On 1 June 2015, the chief investigator requested details of how to obtain a subvention from the National Institute for Health Research. The chief investigator then contacted the Department of Health and requested assistance with the matter and was told that the subvention budget is not used to fund specific study sites and that, as sites for the trial are already signed up for ETCs, they would expect the trust to cover the costs. Keele led negotiations with both the trust and the Clinical Commissioning Groups in the West Midlands (Wolverhampton). Owing to anti-TNF-α falling outside payments by results tariff, both parties argued that they were not funded to support the ETCs associated with this trial. Following negotiation it was agreed that the local Clinical Commissioning Groups and the trust (charitable funds) would fund an equal split of the ETCs. ETCs were approved for Royal Wolverhampton NHS Trust on 19 August 2015 and provisional ETCs agreed for Bart's Health NHS Trust; the trust was told that it would be finalised once R&D approval was given.

Outcome measure results

The original intention was to use a linear mixed-model approach to assess the effects of time, group and time × group. This was not possible as data were only available for eight randomised participants on trial closure. The data for the eight participants are presented. The demographic information is presented in *Appendix 1*. Results from all the measures that were collected at different time points are reported in *Appendix 2*, with the pain manikin drawings presented separately in *Appendix 3*. Resource use results are presented in *Appendix 4* and concomitant medications in *Appendix 5*. Finally, the physiotherapy information is presented in *Appendix 6* and concomitant medications in *Appendix 7*. It is not possible to make any conclusions from these data as no analysis was performed.

Patient and public involvement

The patient and public involvement representative contributed to trial design by commenting on the trial protocol and patient-facing documents, as well as participating in the TSC meetings. Unfortunately, we lost contact with the patient and public involvement representative when trial recruitment was closed.

Comments and feedback from the trial management team and research teams

The trial management team and all sites were asked to reflect on the trial about what worked, and what did not. The following was noted.

Comments from the trial management team

- We would recommend for future studies that a site feasibility questionnaire be designed and sent out at an early stage in the trial to all potential sites to inform them on all aspects of the trial design, to ascertain any potential problems with recruitment and to highlight any logistical challenges that the potential sites may face.
- Documentation was a problem as the TMG had to approve all of the documents used. Members of the group would respond separately, not at all or after the documents had been finalised. In order to provide sufficient clarity and accuracy in the trial documents, we would recommend that documents should only be sent to the lead investigator and PIs, and discussed at individual site team meetings. We would recommend that document meetings, to approve trial documents, should be held on a regular basis and realistic time frames given.
- There were long delays negotiating subcontracts, as much of the contracting discussions focused on whether the academic partners or the clinical sites were responsible for delivering the randomised treatment and physiotherapy to the participants. The contracts needed to be between the NHS sites and the sponsor, with the local universities supporting the process rather than being the contracting party. There needs to be full discussion between the sponsor's contracting department and all academic partners and clinical sites to obtain an early agreement about what the contracts need to include, and how the contracting process should be arranged, so that the academic partners and clinical sites have a clear understanding of their delegated roles and tasks.
- Misattribution of costs was another difficulty for this trial. Sites were asked to provide their own costings on what they required, but some sites had requested funding for their university when it should have been attributed to the NHS site. We would recommend that each site discuss with its finance and R&D department where the funding should be attributed and what costings are required. This needs to be at the application for funding stage.
- Excess treatment costs remained an issue, with no clarity about who was responsible for funding these in the English sites. Commissioners were investing in a study that might not produce savings in the long term, and any savings would be realised within secondary care sites and remain hidden from the commissioners.
- Recruitment was difficult, especially as sciatica participants at this stage in their illness would be managed in primary care, and would not have necessarily been referred to secondary care. These were not insurmountable issues, but early and regular communication between primary and secondary care staff would have been beneficial. Changing patient pathways within the NHS between trial design and completion resulted in challenges at Sherwood Forest Hospitals NHS Foundation Trust. Risk management plans for recruitment were agreed in advance, and implementation should have been timely.
- Difficulties with recruiting patients within 6 months of symptom onset might prove challenging for future research in this area. If the proposed mechanism of action of treatment, and lack of availability of other effective treatments, permits, a longer symptom duration eligibility criterion would be likely to increase recruitment. Several participants who expressed interest in participation had their symptoms for > 6 months. It would have been useful to collect data on exactly how far over the threshold these potential participants were.

- Our experience raises concerns about secondment of service physiotherapists into research roles, in which changes in service demands might result in suspension or termination of their secondment. Availability of dedicated research physiotherapists at sites, or recruitment of research physiotherapists for the specific study, might have reduced staffing issues. Physiotherapists could have been employed directly by the trial rather than seconded, as because of departmental shortages, seconded staff had to resume their previous roles during the agreed seconded period of the trial; this caused major problems and hindered the recruitment of participants in North Wales.

Comments from the Betsi Cadwaladr University Health Board site in the Peter Maddison Rheumatology Centre, Llandudno

- Identifying participants from searches of the general practice record database was not very successful; the uptake from this was very low.
- There were too many components and individuals involved, which affected the success of the trial.
- The trial would have worked better if carried out entirely in primary care.
- Training a research officer with rheumatology experience, or giving a physiotherapist training in biologic treatments, may have been better than involving a physiotherapist and secondary care rheumatology nurses.

Comments from the Betsi Cadwaladr University Health Board Physiotherapy Department

Two main areas of difficulty were identified as barriers to the success of SCIATiC from the research physiotherapist perspective.

1. Recruitment.

    - The search criteria for the general practice record database were not able to be specific enough and were poor in identifying exclusion criteria. At telephone triage, many patients had symptoms for many months, in some cases years, meaning that they were ineligible for the trial. A large proportion of the research physiotherapist's time was wasted telephoning people who were not eligible.
    - Primary care was the main source of patients, but GPs were not universally on board with identifying patients. Not all of the GPs in the participating practices were aware of the trial, so suitable patients may have been missed.

2. Logistics.

    - In the final 6 months from April until September 2016, the time available for the research physiotherapist to contact patients was limited to 2 hours on one afternoon per week. For 5 weeks in December 2015 and January 2016 the research physiotherapist had her hours cut by 50% as she was required to cover the outpatient clinics in the Llandudno physiotherapy department.
    - The number of patients who were available when telephoned in the afternoons was very low.
    - The availability of staff such as research nurses and senior clinicians to support the research physiotherapist was limited as a result of other commitments. It was very difficult to co-ordinate the biological agent counselling, blood tests etc. Because of the restricted staff availability, it was difficult to make timely appointments for eligible participants. It was also difficult to co-ordinate the large number of tests (MRI, T-spot for TB and chest radiography) on 1 day.
    - Owing to the large geographical surface area of BCUHB, some patients had to travel (in pain) for up to 2 hours to attend appointments.

Suggestions for future trials:

- The involvement of the research physiotherapist during the initial planning stage could have helped recruitment and communication. The funding for the post was delayed and then the appointment of the research physiotherapist was later than hoped.
- First-contact physiotherapists were not identified as a source of recruitment. Designing the trial to work with these physiotherapists would have helped identify suitable patients in a timely way.
- Rather than identifying participants from retrospective database searches, clinicians in GP practices could have identified eligible patients during face-to-face consultations and would have been able to check for eligibility before they were invited to participate, resulting in a better conversion rate for trial participation.
- A laminated checklist for each consulting or treatment room containing the inclusion and exclusion criteria may have helped remind staff about the trial.
- Rather than having a single research physiotherapist with limited days and location, it would have been better having physiotherapists in a couple of locations, trained to identify suitable patients on the outpatient waiting list and able to telephone triage to assess eligibility; this would have improved recruitment.

Comments from the Keele team

Trial set-up

- Two key challenges were agreeing the ETCs at one of our two clinical sites, and the merging of two clinical rheumatology services at the time of trial set-up. Both of these challenges delayed the start of the trial significantly.
- Completion of contractual agreements. This trial was a clinical trial of an investigational medicinal product, and Keele clinical trials unit had recent experience of a MHRA inspection in autumn 2015; thus, the Keele team was particularly keen to ensure that all the required contracts and sponsorship arrangements for this trial were clearly in place and appropriate agreements reached about delegation of responsibilities.
- Many of the clinical staff did not feel fully prepared to commence participant recruitment and treatment following the November 2015 training session. Further training was developed and delivered to the research physiotherapists and usual care physiotherapists, supplemented by local working instructions and/or training packs that the Keele team developed. Further discussions were also undertaken with the rheumatological nursing staff involved in the trial in the NHS sites to clarify the study processes and procedures.

Recruitment

- The clinical sites supported by Keele did not have a chance to test the success, or otherwise, of identification and recruitment processes fully because of the short time between open and close to recruitment at their sites (from 11 August to 23 September 2016). However, during this time, the number of potentially eligible patients identified through the GP system searches was smaller than expected.
- There was a reasonable response rate (14 out of 43) to invitations to the trial, and nearly half of these (6 out of 14) were from GPs handing trial information packs to patients in the consultation. It is therefore possible that patients may be more likely to respond if the GP has given them the pack and potentially discussed the trial with them.

Comments from the Sherwood Forest Hospitals NHS Foundation Trust: King's Mill Hospital Rheumatology Department and Back Pain Unit

Recruitment

- Initial recruitment was through back pain clinics within Sherwood Forest Hospitals NHS Foundation Trust.
- It would have been beneficial to have had GP recruitment from the start.
- GPs would have screened for patients on a monthly rolling search.
- Good working relationship with the people from the clinical research network who were identifying participating GPs.
- We could have potentially had five more patients on the study who had given their first consent and had been screened, but were unable to be randomised as the study was closed to recruitment.
- The clinical research network facilitated recruitment through primary care, which became increasingly productive. The average recruitment figures did reflect the higher recruitment rate at the time the study was closed.

Comments from Cardiff

- Very good contact and support form Bangor Trials Unit. Always helpful on the telephone.
- Good support from the PI, as above.
- Flexibility with training packages.
- A major stumbling block was sorting out contracts, which was the main hurdle that, unfortunately, was not overcome in a timely fashion.

Chapter 4 Discussion

Summary of main findings

We have demonstrated that a RCT of adalimumab for persistent sciatica of 3–6 months' duration is acceptable to some participants. The trial methods were feasible in terms of randomisation method and outcome measurement. However, recruitment rates were lower than expected and several other factors contributed to trial termination prior to pilot study completion. We were therefore unable to demonstrate that this trial was feasible. There was a long delay agreeing and exchanging subcontracts with participating centres and sites. The contracting discussions with one site were never concluded and another centre dropped out of the study before recruitment started. There were delays negotiating ETCs for the English centres and sites. We did attempt to recruit additional sites in Wales, but negotiations were not concluded at the time of trial closure. Delays in the contracting process also caused delays in recruiting research staff, in particular the research physiotherapists. In the two sites that did open in time to recruit participants, recruitment was slow. In one site, the sciatica management pathway changed around the time that it opened to recruitment. This site initially only relied on referrals to its secondary care musculoskeletal service, but later involved the primary care research network, which was starting to identify participants just before trial closure. In the other site there were operational issues identifying the research physiotherapist resource. This site relied on retrospective GP record review to identify potential participants and although large numbers of invitations were sent to potential participants, there was a low rate of uptake with only a small proportion seen for an initial assessment, and entered into the trial. We were in the process of increasing the number of GP practices within the North Wales area to assist with increasing recruitment; this was not concluded prior to the trial closure. Recruitment was improving just before the trial was shut down with five potential participants ready to be recruited within the following month.

Strengths and weaknesses

The trial methods, in terms of randomisation method and outcome measurement, worked smoothly but for only eight participants, so it is not possible to claim that the methods were feasible. An internal pilot study was planned, but unfortunately we were unable to recruit sufficient numbers.

We had modelled the numbers of eligible participants for our recruitment projections on the ATLAS cohort study.[39] However, we made unrealistic assumptions about the numbers of identified participants who would be willing to participate in a clinical trial of an investigational medicinal product. Although we identified large numbers of potential participants, only small numbers returned reply slips indicating a willingness to participate. It was not known why eligible participants did not wish to participate. Presumably, some found the trial procedures too burdensome, such as the complex two-stage recruitment process, whereas others did not want to participate in a RCT, especially in a clinical trial of an investigational medicinal product involving a medication with known potential side effects. The ATLAS study cohort was led by the team at Keele University and recruited 610 participants in 23 months.[60] The two clinical sites supported by Keele signed their contracts just prior to trial closure. Although potential participants had started to be identified, there was insufficient time to recruit them. Because of this, it was not possible to compare rates of recruitment into the RCT with those found in the ATLAS cohort study, nor the more recent HTA-funded Sciatica Outcomes in Primary Care trial using similar methods of identifying participants. One site in east London dropped out of the trial just before recruitment began because the PI had concerns about patient safety. The PIs in the other sites reviewed the safety risks to potential participants and felt that these risks were justified and that measures were in place to mitigate, detect and address any adverse effects. Although there were only short delays in obtaining research permissions and finalising the trial contract with the funder, there were very long delays negotiating subcontracts with three of the sites. The difficulty of

achieving clarity of delegation of functions, and clarity about what needed to be in the different contracts (university to university vs. university to NHS trusts) are key learning experiences from this trial. Negotiations concerning ETCs in England were protracted and complex, which added to the delay negotiating contracts and setting up sites.

Comparison with previous literature

The previous systematic review of biological agents for sciatica found a small number of RCTs and other studies with small numbers of participants recruited.[21] Many of these studies also had poor rates of recruitment, especially in the UK NHS.[24]

Implications for future research

A number of factors contributed to the lack of recruitment to the trial. There were delays in contracting, the process for identifying and recruiting participants was inefficient, there were delays in site set-up and a lack of investigator engagement (possibly because of a lack of equipoise). After the London centre withdrew, we asked the other PIs whether or not the research question was still in equipoise. They all agreed that the risk of infection from the dose of drug administered in this trial was acceptable, and that they were still in equipoise.

In order to reduce delays in the contracting process, there needs to be an early agreement about what the contracts need to include, and how the contracting process should be arranged, so that the academic partners and clinical sites have a clear understanding of their delegated roles and tasks. Early discussions about site requirements, perhaps using a site feasibility questionnaire, early dialogue with sites' R&D departments and the early appointment of research staff in each site would facilitate trial set-up.

We are unable to make any recommendations for future practice in this area because of a lack of trial results. Without any results from the internal pilot study, it is difficult to make recommendations for future research in this area. It may be that there is insufficient equipoise around the question of adalimumab for sciatica among patients and some clinicians. However, this would need to be addressed in further qualitative research. The two-stage recruitment process was complicated and not feasible. We had modelled the number of potentially eligible patients on results from the ATLAS cohort study. However, ATLAS did not use the same two-stage process, nor did it rely on retrospective searches of GP records, but rather relied on the identification and invitation of eligible patients who were currently consulting their GP for sciatica. The same recruitment process for ATLAS, which relies on GPs entering relevant diagnostic Read codes into their computer systems, triggering a 'pop-up' reminder about sending eligible patients to dedicated clinics for further assessment and eligibility checking, has worked in the Sciatica Outcomes in Primary Care (SCOPiC) trial.[61] Similar recruitment methods were going to be used in the two sites supported by the Keele co-applicants. Unfortunately, because of delays in finalising contracts and setting up sites there was insufficient time to recruit any participants and to test these recruitment methods before trial closure. So, it is still not possible to say whether or not the use of the recruitment method used in the SCOPiC trial would be feasible for a similar RCT in the NHS testing an investigational medicinal product.

A trial of biological therapy in patients with sciatica still needs to be done, but would require a clearer contracting process, qualitative research to ensure that patients would be willing to participate and simpler recruitment methods.

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Contributions of authors

Nefyn H Williams (Clinical Senior Lecturer in General Practice) was the chief investigator and grant holder, was responsible for study design, conduct and analysis, led the writing of *Chapters 1*, *2* and *4*, contributed to all other chapters, led the discussions of the implications of study findings and had overall responsibility for the study and final report.

Alison Jenkins (Trial Manager) was responsible for overseeing day-to-day conduct, contributed to all chapters of the report and contributed to the discussion of the implications of study findings.

Nia Goulden (Trial Statistician) conducted the statistical analysis for the trial, led the writing of *Chapter 3* and gave feedback on other chapters of the report.

Zoe Hoare (Principal Trial Statistician) gave input to study design, was responsible for the statistical analysis design, provided methodological oversight and support for the trial statistician, and contributed to the discussion of the implications of study findings.

Dyfrig A Hughes (Professor of Health Economics) was a co-investigator, contributed to the study design, was responsible for the economic evaluation, and commented on all chapters of the final report and to the discussion of the implications of study findings.

Eifiona Wood (Senior Research Fellow in Pharmacoeconomics) was the trial health economist, commented on all chapters of the final report and contributed to the discussion of the implications of study findings.

Nadine E Foster (National Institute for Health Research Professor of Musculoskeletal Health in Primary Care) was a co-investigator, contributed to methodology and study design, commented on all chapters of the final report and contributed to discussion of the implications of study findings.

David A Walsh (Professor of Rheumatology) was a co-investigator, was responsible for study design, provided methodological oversight throughout the study, commented on all chapters of the final report and contributed to the discussion of the implications of study findings.

Dawn Carnes (Senior Lecturer in Musculoskeletal Health) was a co-investigator, and contributed to the methodology and study design.

Valerie Sparkes (Reader in Arthritis Research, Director of Impact and Innovation) was a co-investigator, contributed to the methodology and study design, and provided physiotherapy expertise.

Elaine M Hay (Professor of Community Rheumatology) contributed to the methodology and study design.

John Isaacs (Professor of Clinical Rheumatology) gave input to the study design.

Kika Konstantinou (Spinal Physiotherapy Specialist) was a co-investigator, contributed to methodology and study design, provided physiotherapy expertise, commented on all chapters of the final report and contributed to the discussion of the implications of study findings.

Dylan Morrissey (Consultant Physiotherapist, Clinical Reader) was a co-investigator, contributed to the methodology and study design, and provided physiotherapy expertise.

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Data sharing statement

All available data are included as appendices or can be obtained from the corresponding author.

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Appendix 1 Demographic information for each of the eight randomised participants

	Treatment group, participant ID							
	Placebo				Adalimumab			
Characteristic	1	2	3	4	5	6	7	8
Site	Llandudno General Hospital	Llandudno General Hospital	King's Mill Hospital	King's Mill Hospital	Llandudno General Hospital	King's Mill Hospital	King's Mill Hospital	King's Mill Hospital
Age (years)	46	72	64	59	20	62	68	41
Ethnicity	Welsh	British	English	English	Welsh	English	English	English
Sex	Male	Male	Female	Male	Female	Female	Male	Female
Height (cm)	183	180	159	175	167	170	186	164
Weight (kg)	90	83	96	78	88	134	93	76
Employment status	FT	PT	Retired	FT	PT	FT	Retired	FT
Absent from work as a result of sciatica?	Yes	No	N/A	Yes	Yes	Yes	N/A	Yes
Sickness certificate?	Yes	No	N/A	Yes	Yes	Yes	N/A	Yes

FT, full-time; ID, identification; N/A, not applicable; PT, part-time.

Appendix 2 Scores from all of the outcome measures for each of the eight randomised participants

	Treatment group, participant ID							
	Placebo				Adalimumab			
Outcome measure	1	2	3	4	5	6	7	8
ODI								
First clinical assessment	66	36	78	66	76	54	36	60
Second clinical assessment	80	48	76	46	76	54	36	64
6-week follow-up	18	38	72	34	76	64	20	58
6-month follow-up	6	Not completed	74	Not completed	Not completed	64	Not Completed	Not completed
Global Assessment								
Back at 6-week follow-up	Much better	No change	Much worse	Much better	Worse	Better	No change	Worse
Leg at 6-week follow-up	Better	No change	Much worse	Much better	Worse	No change	No change	No change
Back at 6-month follow-up	Much better	Not completed	Better	Not completed	Not completed	Better	Not completed	Not completed
Leg at 6-month follow-up	Better	Not completed	No change	Not completed	Not completed	No change	Not completed	Not completed
Sciatica Bothersomeness Index								
Pain in leg at first treatment	5	4	6	6	5	4	4	6
Numbness or tingling in leg, foot or groin at first treatment	5	5	3	6	4	6	4	5
Weakness in foot or leg at first treatment	5	4	0	0	6	6	4	5
Back or leg pain while sitting at first treatment	4	6	6	6	5	4	4	5
Pain in leg at 6-week follow-up	2	4	6	3	5	4	6	5
Numbness or tingling in leg, foot or groin at 6-week follow-up	4	5	6	3	3	6	6	5
Weakness in foot or leg at 6-week follow-up	5	3	6	4	5	6	6	5

	Treatment group, participant ID							
	Placebo				Adalimumab			
Outcome measure	1	2	3	4	5	6	7	8
Back or leg pain while sitting at 6-week follow-up	2	5	5	2	6	4	4	5
Pain in leg at 6-month follow-up	0	Not completed	5	Not completed	Not completed	4	Not completed	Not completed
Numbness or tingling in leg, foot or groin at 6-month follow-up	4	Not completed	3	Not completed	Not completed	6	Not completed	Not completed
Weakness in foot or leg at 6-month follow-up	4	Not completed	0	Not completed	Not completed	6	Not completed	Not completed
Back or leg pain while sitting at 6-month follow-up	1	Not completed	6	Not completed	Not completed	4	Not completed	Not completed
EQ-5D-5L								
State at first treatment	33333	32231	43452	33342	33543	45433	32332	32442
Score at first treatment	0.63	0.76	0.15	0.46	0.31	0.38	0.67	0.37
Scale at first treatment	70	55	40	65	40	25	55	30
State at 6-week follow-up	21131	22331	43453	11231	43542	43434	21232	32332
Score at 6-week follow-up	0.88	0.76	0.12	0.88	0.19	0.19	0.75	0.67
Scale at 6-week follow-up	80	65	30	80	40	40	50	35
State at 6-month follow-up	21221	Not completed	43452	Not completed	Not completed	43434	Not completed	Not completed
Score at 6-month follow-up	0.84	Not completed	0.15	Not completed	Not completed	0.19	Not completed	Not completed
Scale at 6-month follow-up	85	Not completed	50	Not completed	Not completed	40	Not completed	Not completed

	Treatment group, participant ID							
	Placebo				Adalimumab			
Outcome measure	1	2	3	4	5	6	7	8
Hospital Anxiety and Depression Scale								
Anxiety score at first treatment	12	3	6	4	15	17	10	10
Depression score at first treatment	7	4	10	13	9	14	7	10
Total score at first treatment	19	7	16	17	24	31	17	20
Anxiety score at 6-week follow-up	2	3	12	9	11	13	5	10
Depression score at 6-week follow-up	3	3	16	6	13	12	5	10
Total score at 6-week follow-up	5	6	28	15	24	25	10	20
Anxiety score at 6-month follow-up	2	Not completed	6	Not completed	Not completed	13	Not completed	Not completed
Depression score at 6-month follow-up	1	Not completed	10	Not completed	Not completed	12	Not completed	Not completed
Total score at 6-month follow-up	3	Not completed	16	Not completed	Not completed	25	Not completed	Not completed
Keele STarT Back Screening Tool								
First treatment	6	5	7	3	8	8	6	5
Subscore at first treatment	3	1	4	2	4	4	3	4
Tampa Scale of Kinesiophobia								
First treatment	45	Not completed	40	56	42	40	44	41
6-week follow-up	34	32	41	47	48	42	40	41
6-month follow-up	38	Not completed	40	Not completed	Not completed	43	Not completed	Not completed

Outcome measure	Treatment group, participant ID							
	Placebo				Adalimumab			
	1	2	3	4	5	6	7	8
Group Likert scale								
6-week follow-up	Equally likely to be in the 0.9% sodium chloride injection group or the adalimumab injection group	Equally likely to be in the 0.9% sodium chloride injection group or the adalimumab injection group	More likely to be in the 0.9% sodium chloride injection group	Equally likely to be in the 0.9% sodium chloride injection group or the adalimumab injection group	More likely to be in the adalimumab injection group	Equally likely to be in the 0.9% sodium chloride injection group or the adalimumab injection group	Definitely in the 0.9% sodium chloride injection group	More likely to be in the adalimumab injection group
6-month follow-up	More likely to be in the 0.9% sodium chloride injection group	Not completed	More likely to be in the 0.9% sodium chloride injection group	Not completed	Not completed	Equally likely to be in the 0.9% sodium chloride injection group or the adalimumab injection group	Not completed	Not completed
PSEQ								
First treatment	26	48	8	17	9	14	30	9
6-week follow-up	41	34	3	46	7	21	37	9
6-month follow-up	50	Not completed	10	Not completed	Not completed	21	Not completed	Not completed
RMDQ								
Back at first treatment	21	Not completed	19	0	21	23	1	0
Leg at first treatment	21	Not completed	18	19	21	23	19	24
Back at 6-week follow-up	3	Not completed	20	7	21	21	0	0
Leg at 6-week follow-up	Not completed	Not completed	16	10	18	22	9	23
Back at 6-month follow-up	2	Not completed	19	Not completed	Not completed	21	Not completed	Not completed
Leg at 6-month follow-up	3	Not completed	18	Not completed	Not completed	21	Not completed	Not completed

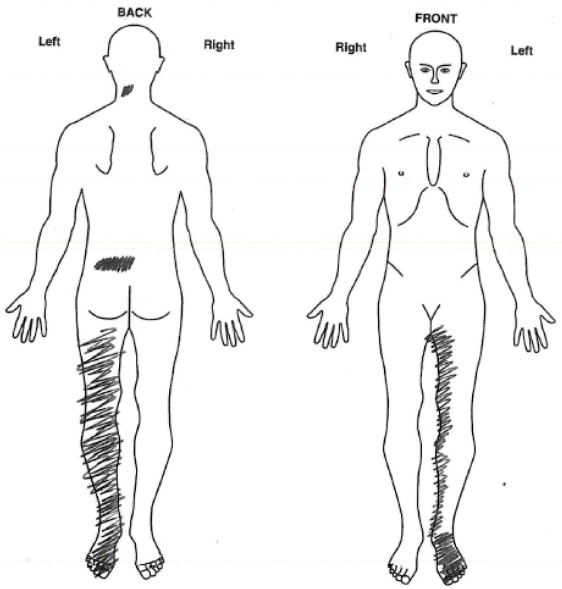
ID, identification.

Appendix 3 Completed pain manikins for all eight participants randomised

Participant 1 First Clinical Assessment

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.

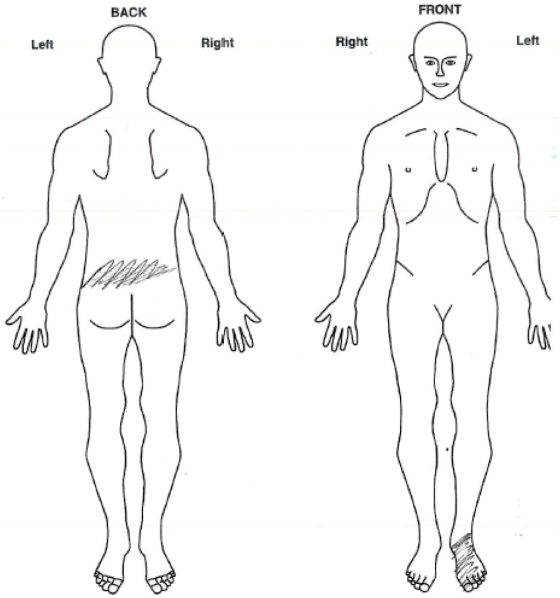


If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a tick in this box ☐

[redacted]

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one da longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do r** pain due to feverish illness such as flu.



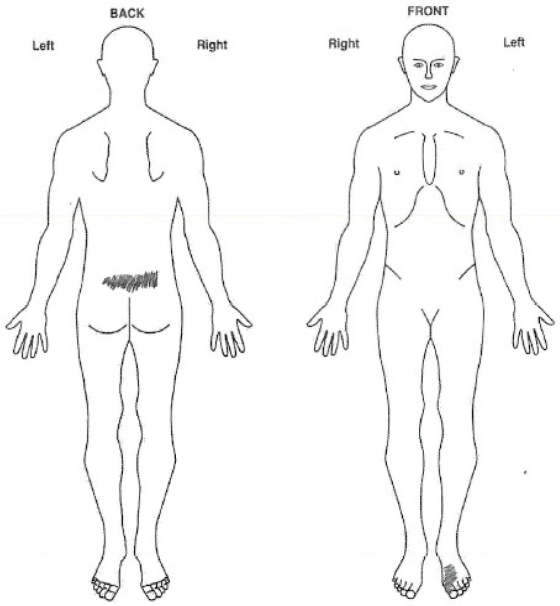
If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a cross in this box ☐

[redacted]

Participant 1 Six Month Follow-up

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a cross in this box ☐

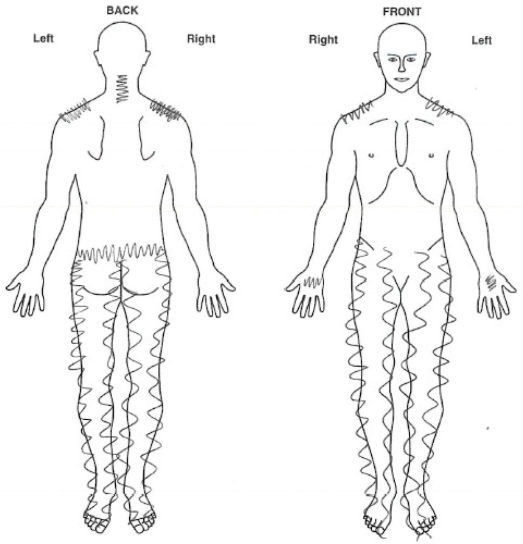
SCIATiC 6 month CRF v 3 Bilingual EQ5D5L 19th June 2015 and HADS 9th July 2015 HTA Project: 12/201/02

[redacted]

Participant 2 First Clinical Assessment

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a cross in this box ☐

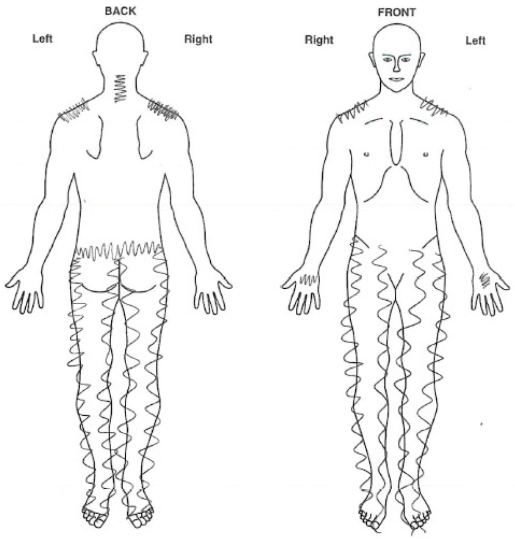
SCIATiC 6 week v3 Bilingual EQ5D5L 19th June 2015 and HADS 9th July 2015 HTA Project: 12/201/02

[redacted]

Participant 2 Six Week Follow-up

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not*** **had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a cross in this box ☐

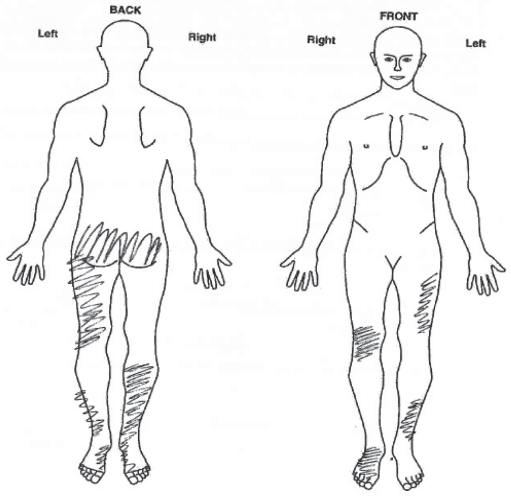
SCIATIC 6 week v3 Bilingual EQ5D5L 19th June 2015 and HADS 9th July 2015 HTA Project: 12/201/02

[redacted]

Participant 3 First Clinical Assessment

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not*** **had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a tick in this box ☑

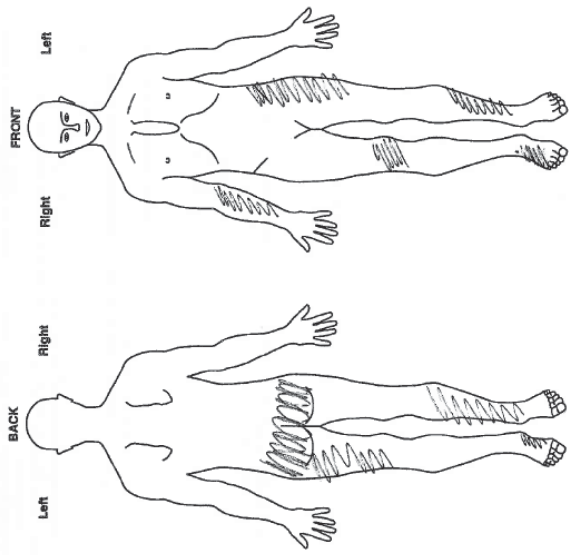
SCIATIC Baseline v 2 6th May 2015 HTA Project: 12/201/02

[redacted]

Participant 3 Six Month Follow-up

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the last 4 weeks. By pain we also mean ache, discomfort or stiffness. Please do not includ pain due to feverish illness such as flu.



If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a cross in this box X error

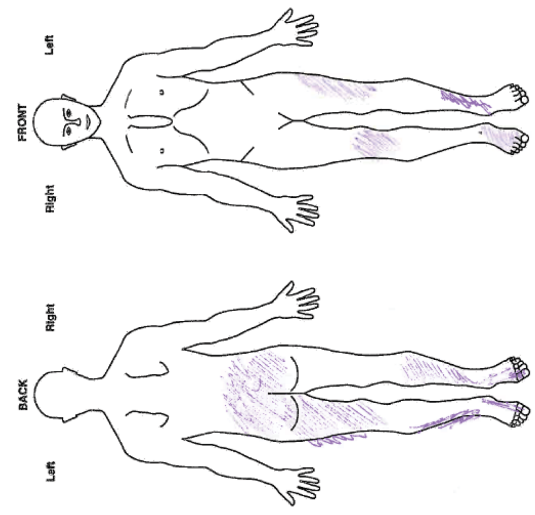
SCIATIC 6 month CRF v 3 5th June 2015 HTA Project: 12/201/02

[redacted]

Participant 3 Six Week Follow-up

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the last 4 weeks. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a cross in this box ☐

SCIATIC 6 week v 3 5th June 2015 HTA Project: 12/201/02

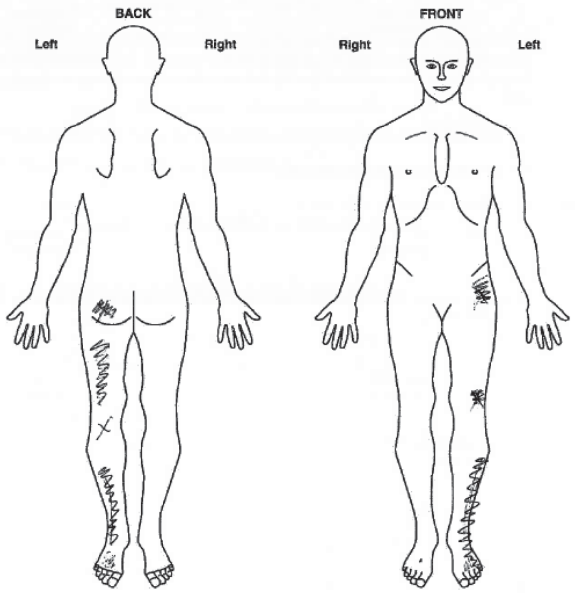
[redacted]

Participant 4 First Clinical Assessment

P

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a tick in this box ☐

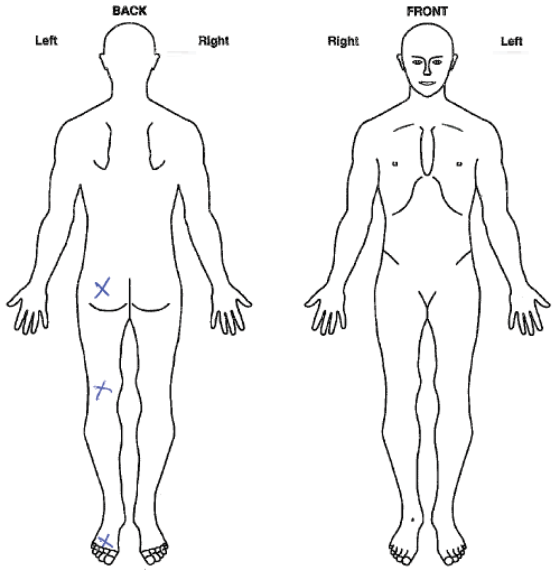
SCIATiC Baseline v 2 6th May 2015 HTA Project: 12/201/02

[redacted]

Participant 4 Six Week Follow-up

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a cross in this box ☐

SCIATiC 6 week v 3 5th June 2015 HTA Project: 12/201/02

[redacted]

Participant 5 First Clinical Assessment

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only ref
to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or
longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** inclu
pain due to feverish illness such as flu.

If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks,
please put a tick in this box ☐

SCIATIC Baseline v2 Bilingual EQ5D5L dated 19th June 2015 and HADS 9th July 2015 HTA Project: 12/201/02

Participant 5 Six Week Follow-up

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer
to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or
longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include
pain due to feverish illness such as flu.

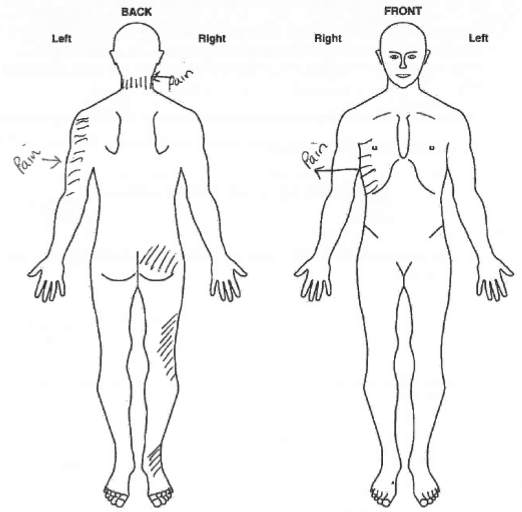
If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks,
please put a cross in this box ☐

SCIATIC 6 week v3 Bilingual EQ5D5L 19th June 2015 and HADS 9th July 2015 HTA Project: 12/201/02

Participant 6 First Clinical Assessment

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



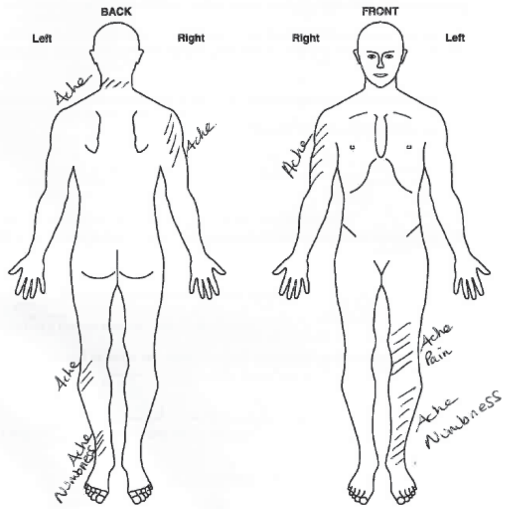
If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a tick in this box ☐

SCIATIC Baseline v 2 6th May 2015 HTA Project: 12/201/02

Participant 6 Six Week Follow-up

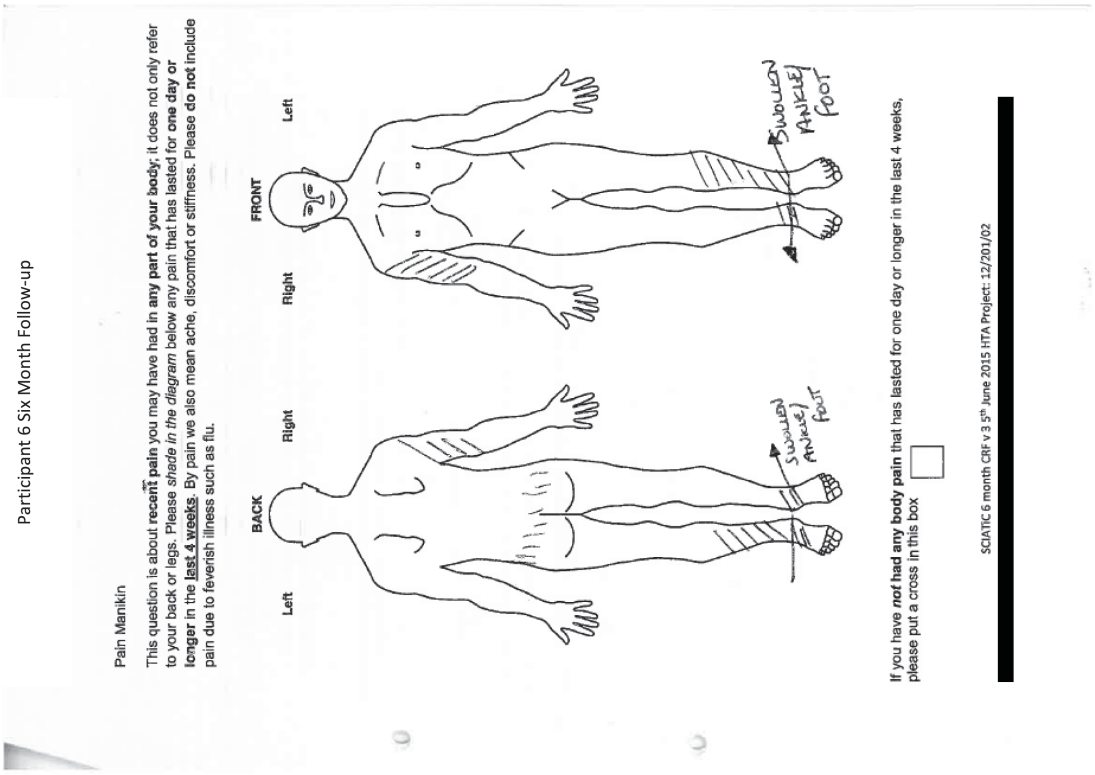
Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a cross in this box ☐

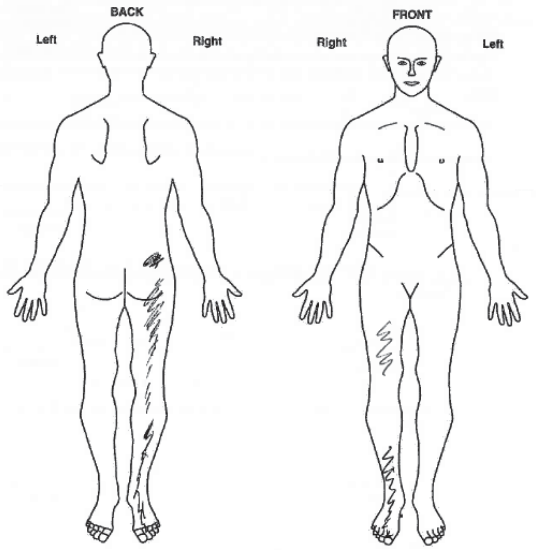
SCIATIC 6 week v 3 5th June 2015 HTA Project: 12/201/02



Participant 7 First Clinical Assessment

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, **please put a tick in this box** ☐

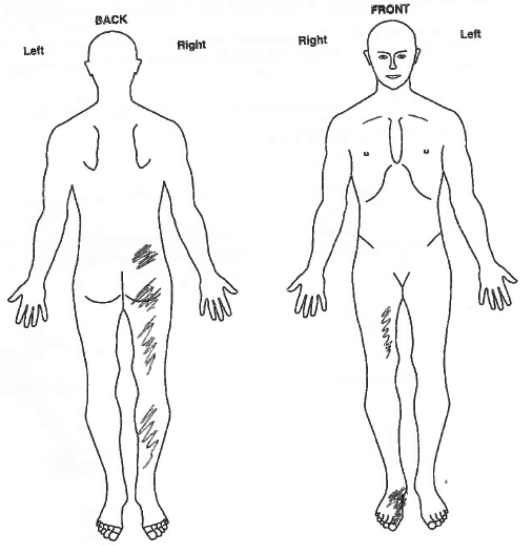
SCIATIC Baseline v 2 6th May 2015 HTA Project: 12/201/02

[redacted]

Participant 7 Six Week Follow-up

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.



If you have ***not* had any body pain** that has lasted for one day or longer in the last 4 weeks, **please put a cross in this box** ☐

SCIATIC 6 week v 3 5th June 2015 HTA Project: 12/201/02

[redacted]

Participant 8 First Clinical Assessment

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.

If you have ***not*** **had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a tick in this box ☐

SCIATIC Baseline v 2 6th May 2015 HTA Project: 12/201/02

Participant 8 Six Week Follow-up

Pain Manikin

This question is about **recent pain** you may have had in **any part of your body**; it does not only refer to your back or legs. Please *shade in the diagram* below any pain that has lasted for **one day or longer** in the **last 4 weeks**. By pain we also mean ache, discomfort or stiffness. Please **do not** include pain due to feverish illness such as flu.

If you have ***not*** **had any body pain** that has lasted for one day or longer in the last 4 weeks, please put a cross in this box ☐

SCIATIC 6 week v 3 5th June 2015 HTA Project: 12/201/02

Appendix 4 Results from the Resource Use Questionnaire for all eight randomised participants

	Treatment group, participant ID							
	Placebo				Adalimumab			
Time point of assessment	1	2	3	4	5	6	7	8
First clinical assessment								
Bought medicines from pharmacy or other retailer?	Yes	No	No	No	Yes	No	No	Yes
Cost to nearest pound (reasons related to sciatica)	20	N/A	N/A	N/A	36	N/A	N/A	100
Cost to nearest pound (other reasons)	0	N/A	N/A	N/A	0	N/A	N/A	0
Did you travel by private car for any of your visits?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Miles (reasons related to sciatica)	25	0	22	3	N/A	28	3	10
Miles (other reasons)	0	0	0	0	0	0	0	0
Did you travel by bus, train or taxi for any of your visits to GP surgeries or hospital visits?	No	No	No	No	No	No	No	No
Cost (reasons related to sciatica)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cost (other reasons)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number of GP surgery visits (reasons related to sciatica)	0	2	2	3	12	3	3	7
Number of GP surgery visits (other reasons)	0	0	0	0	0	0	0	0
Number of GP out-of-hours surgery visits (reasons related to sciatica)	0	0	0	0	0	0	0	0
Number of GP out-of-hours surgery visits (other reasons)	0	0	0	0	0	0	0	0
Number of GP home visits (reasons related to sciatica)	0	0	0	0	0	0	0	0
Number of GP home visits (other reasons)	0	0	0	0	0	0	0	0
Number of A&E visits (reasons related to sciatica)	0	0	0	0	1	0	0	0
Number of A&E visits (other reasons)	0	0	0	0	0	0	0	0
Number of outpatient clinic visits (reasons related to sciatica)	0	0	3	0	9	3	0	0
Number of outpatient clinic visits (other reasons)	0	0	0	0	0	0	0	0
Number of outpatient day-case visits (reasons related to sciatica)	0	0	0	0	0	0	0	0

	Treatment group, participant ID							
	Placebo				Adalimumab			
Time point of assessment	1	2	3	4	5	6	7	8
Number of outpatient day-case visits (other reasons)	0	0	0	0	0	0	0	0
Number of inpatient visits	0	0	0	0	0	0	0	0
Number of visits to physiotherapist	5	0	0	0	0	0	0	0
Cost (£)	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number of acupuncture sessions	0	0	0	0	0	0	0	0
Cost (£)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number of visits to osteopath/ chiropractor	0	0	0	1	0	0	0	0
Cost (£)	N/A	N/A	N/A	37	N/A	N/A	N/A	N/A
Number of other services outside hospital	0	0	0	0	0	0	0	0
Cost (£)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Your number of days off (to nearest half day) (reasons related to sciatica)	27	0	0	0	80	84	0	0
Lost earnings (to nearest pound) (reasons related to sciatica)	0	N/A	N/A	N/A	600	0	N/A	N/A
Your number of days off (to nearest half day) (other reasons)	0	0	0	0	0	0	0	0
Lost earnings (to nearest pound) (other reasons)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Family member/friend number of days off (to nearest half day) (reasons related to sciatica)	0	0	0	0	15	0	0	0
Family member/friend lost earnings (to nearest pound) (reasons related to sciatica)	N/A	N/A	N/A	N/A	700	N/A	N/A	N/A
Family member/friend number of days off (to nearest half day) (other reasons)	0	0	0	0	0	0	0	0
Family member/friend lost earnings (to nearest pound) (other reasons)s	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6-week follow-up								
Bought medicines from pharmacy or other retailer?	No	Not completed	Yes	No	Yes	No	No	Yes
Cost to nearest pound (reasons related to sciatica)	N/A	Not completed	50	N/A	84	N/A	N/A	100
Cost to nearest pound (other reasons)	N/A	Not completed	0	N/A	0	N/A	N/A	0
Did you travel by private car for any of your visits?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Miles (reasons related to sciatica)	2	40	60	N/A	N/A	20	4	20
Miles (other reasons)	0	0	0	0	0	0	0	0

	Treatment group, participant ID							
	Placebo				Adalimumab			
Time point of assessment	1	2	3	4	5	6	7	8
Did you travel by bus, train or taxi for any of your visits to GP surgeries or hospital visits?	No	No	No	No	No	No	No	No
Cost (reasons related to sciatica)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cost (other reasons)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number of GP surgery visits (reasons related to sciatica)	0	0	1	0	2	0	0	7
Number of GP surgery visits (other reasons)	0	0	0	0	0	0	0	0
Number of GP out-of-hours surgery visits (reasons related to sciatica)	0	0	0	0	0	0	0	0
Number of GP out-of-hours surgery visits (other reasons)	0	0	0	0	0	0	0	0
Number of GP home visits (reasons related to sciatica)	0	0	0	0	0	0	0	0
Number of GP home visits (other reasons)	0	0	0	0	0	0	0	0
Number of A&E visits (reasons related to sciatica)	0	0	1	0	0	0	0	0
Number of A&E visits (other reasons)	0	0	0	0	0	0	0	0
Number of outpatient clinic visits (reasons related to sciatica)	0	0	0	0	2	0	2	0
Number of outpatient clinic visits (other reasons)	0	0	0	0	0	0	0	0
Number of outpatient day-case visits (reasons related to sciatica)	0	0	0	0	0	0	0	0
Number of outpatient day-case visits (other reasons)	0	0	0	0	0	0	0	0
Number of inpatient visits	0	0	0	0	0	0	0	0
Number of visits to physiotherapist	0	4	0	0	0	0	0	0
Cost (£)	N/A	0	N/A	N/A	N/A	N/A	N/A	N/A
Number of acupuncture sessions	0	0	0	0	0	0	0	0
Cost (£)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number of visits to osteopath/ chiropractor	0	0	0	0	0	0	0	0
Cost (£)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number of other services outside hospital	0	0	0	0	0	0	0	0
Cost (£)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Treatment group, participant ID							
	Placebo				Adalimumab			
Time point of assessment	1	2	3	4	5	6	7	8
Your number of days off (to nearest half day) (reasons related to sciatica)	0	0	0	0	120	42	0	18
Lost earnings (to nearest pound) (reasons related to sciatica)	0	0	0	0	950	0	0	0
Your number of days off (to nearest half day) (other reasons)	0	0	0	0	0	0	0	0
Lost earnings (to nearest pound) (other reasons)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Family member/friend number of days off (to nearest half day) (reasons related to sciatica)	0	0	0	0	2	0	0	0
Family member/friend lost earnings (to nearest pound) (reasons related to sciatica)	N/A	N/A	N/A	N/A	240	N/A	N/A	N/A
Family member/friend number of days off (to nearest half day) (other reasons)	0	0	0	0	0	0	0	0
Family member/friend lost earnings (to nearest pound) (other reasons)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6-month follow-up visits								
Bought medicines from pharmacy or other retailer?	Yes	Not completed	No	Not completed	Not completed	No	Not completed	Not completed
Cost to nearest pound (reasons related to sciatica)	2	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed
Cost to nearest pound (other reasons)	N/A	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Did you travel by private car for any of your visits?	No	Not completed	Yes	Not completed	Not completed	Yes	Not completed	Not completed
Miles (reasons related to sciatica)	N/A	Not completed	20	Not completed	Not completed	20	Not completed	Not completed
Miles (other reasons)	N/A	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Did you travel by bus, train or taxi for any of your visits to GP surgeries or hospital visits?	No	Not completed	No	Not completed	Not completed	No	Not completed	Not completed
Cost (reasons related to sciatica)	N/A	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed
Cost (other reasons)	N/A	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed
Number of GP surgery visits (reasons related to sciatica)	0	Not completed	2	Not completed	Not completed	0	Not completed	Not completed
Number of GP surgery visits (other reasons)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of GP out-of-hours surgery visits (reasons related to sciatica)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed

	Treatment group, participant ID							
	Placebo				Adalimumab			
Time point of assessment	1	2	3	4	5	6	7	8
Number of GP out-of-hours surgery visits (other reasons)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of GP home visits (reasons related to sciatica)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of GP home visits (other reasons)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of A&E visits (reasons related to sciatica)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of A&E visits (other reasons)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of outpatient clinic visits (reasons related to sciatica)	0	Not completed	2	Not completed	Not completed	0	Not completed	Not completed
Number of outpatient clinic visits (other reasons)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of outpatient day-case visits (reasons related to sciatica)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of outpatient day-case visits (other reasons)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of inpatient visits	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Number of visits to physiotherapist	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Cost (£)	N/A	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed
Number of acupuncture sessions	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Cost (£)	N/A	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed
Number of visits to osteopath/ chiropractor	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Cost (£)	N/A	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed
Number of other services outside hospital	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Cost (£)	N/A	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed
Your number of days off (to nearest half day) (reasons related to sciatica)	0	Not completed	0	Not completed	Not completed	43	Not completed	Not completed
Lost earnings (to nearest pound) (reasons related to sciatica)	N/A	Not completed	N/A	Not completed	Not completed	0	Not completed	Not completed
Your number of days off (to nearest half day) (other reasons)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Lost earnings (to nearest pound) (other reasons)	N/A	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed

	Treatment group, participant ID							
	Placebo				Adalimumab			
Time point of assessment	1	2	3	4	5	6	7	8
Family member/friend number of days off (to nearest half day) (reasons related to sciatica)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Family member/friend lost earnings (to nearest pound) (reasons related to sciatica)	N/A	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed
Family member/friend number of days off (to nearest half day) (other reasons)	0	Not completed	0	Not completed	Not completed	0	Not completed	Not completed
Family member/friend lost earnings (to nearest pound) (other reasons)	N/A	Not completed	N/A	Not completed	Not completed	N/A	Not completed	Not completed

A&E, accident and emergency; ID, identification; N/A, not applicable.

Appendix 5 Concomitant medications for all eight randomised participants

	Treatment group, participant ID							
	Placebo				Adalimumab			
Medication	1	2	3	4	5	6	7	8
Concomitant medications first clinical assessment								
Number of concomitant medications	0	5	8	4	9	5	10	0
Medication name		• Capasal Therapeutic Shampoo (Dermal Laboratories Ltd, Hitchin, UK) as required • Esomeprazole 20 mg once daily • Mebeverine 135 mg once daily • Solifenacin (Vesicare®; Astellas Pharma Ltd, Tokyo, Japan) 5 mg once daily • Pregabalin 75 mg once daily	• Omeprazole 20 mg once daily • Simvastatin 40 mg once daily • Ramipril 10 mg once daily • Venlafaxine 75 mg once daily • Aspirin 75 mg once daily • Metformin 500 mg once daily • Gliclazide 40 mg twice daily • Temazepam 20 mg once daily	• Lansoprazole 30 mg once daily • Gabapentin • Paracetamol 1 g every 4 hours • Naproxen 250 mg	• Thyroxine 75 µg once daily • Omeprazole 20 mg once daily • Loestrin® (Galen Ltd, Craigavon, UK) once daily • Sertraline 100 mg once daily • Diazepam 2 mg three times daily • Gabapentin 300 mg three times daily • ZOMORPH (Ethypharm UK Ltd, High Wycombe, UK) 20 mg twice daily • Paracetamol 1 g three times daily • Ibuprofen 40 mg three times daily	• Gabapentin 600 mg three times daily • Paracetamol 1 g as required • Bendroflumethiazide 2.5 mg once daily • Losartan 100 mg once daily • Bezafibrate 400 mg once daily	• Zapain (Concordia International Rx UK Ltd, London, UK) 30 mg four times daily • Diclofenac 50 mg three times daily • Diazepam 2 mg three times daily • Amitriptyline 10 mg once daily • Lisinopril 20 mg once daily • Lixisenatide (Lyxumia®; Sanofi, Paris, France) 20 µg once daily • Felodipine 2.5 mg once daily • Gliclazide 80 mg twice daily • Metformin 850 mg twice daily • Atorvastatin 40 mg once daily	

	Treatment group, participant ID							
	Placebo				Adalimumab			
Medication	1	2	3	4	5	6	7	8
Concomitant medications first treatment								
Number of concomitant medications	0	5	0	0	11	5	0	0
Medication name		• Capasal therapeutic shampoo, as required • Esomeprazole 20 mg once daily • Mebeverine 135 mg once daily • Solifenacin 5 mg once daily • Pregabalin 275 mg once daily			• Paracetamol 1 g as required • Ibuprofen 400 mg three times daily • Thyroxine 75 µg once daily • Omeprazole 20 mg once daily • Loestrin once daily • Sertraline 100 mg once daily • Diazepam 2 mg three times daily • Gabapentin 300 mg 3 times daily • ZOMORPH 20 mg twice daily, then ZOMORPH 20 mg once daily, then ZOMORPH 30 mg once daily	• Gabapentin 600 mg three times daily • Paracetamol 1 g every 4 hours • Bendroflumethiazide 2.5 mg once daily • Losartan 100 mg once daily • Bezafibrate 400 mg once daily		

	Treatment group, participant ID							
	Placebo				Adalimumab			
Medication	1	2	3	4	5	6	7	8
Concomitant medications second treatment								
Number of concomitant medications	0	5	0	0	0	0	0	0
Medication name		• Capasal therapeutic shampoo as required • Omeprazole 20 mg once daily • Mebeverine 135 mg once daily • Solifenacin 5 mg once daily • Pregabalin 300 mg once daily						

ID, identification.

Appendix 6 Physiotherapy treatment received for all eight randomised participants

Physiotherapy treatment	Treatment group, participant ID							
	Placebo				Adalimumab			
	1	2	3	4	5	6	7	8
Number of physiotherapy courses	1	Not completed	4	6	1	6	6	4
Advice, education and reassurance?	0	Not completed	4	5	5	4	5	5
Medication usage discussion/review?	0	Not completed	1	0	2	1	2	0
Specific exercise: stability	0	Not completed	2	2	0	3	3	0
Specific exercise: McKenzie	1	Not completed	2	4	0	2	3	0
Specific exercise: neural glides	1	Not completed	0	4	0	0	3	1
Specific exercise: other	1	Not completed	2	1	1	4	3	2
Details	Gluteus maximus maximum stretch	Not completed	Mobilisation exercises, reduced exercise	Strength and relaxation	Posture	Mobilisation exercises, balance	Iliotibial band, piriformis stretch	General mobility and flare up
Joint mobilisations/ manipulations	0	Not completed	0	0	0	0	0	0
Soft tissue techniques	0	Not completed	0	0	0	0	0	0
Other treatment	0	Not completed	2	4	5	0	4	3
Details	N/A	Not completed	Relaxation CD, paired walking	Posture limitations and postural structure	Acupuncture	N/A	Advice on overactivity, swimming, use of heat	Relaxation and visualisation
Action plan for relapse discussed	Not completed	Not completed	2	Not completed	Not completed	4	1	Not completed

Physiotherapy treatment	Treatment group, participant ID							
	Placebo				Adalimumab			
	1	2	3	4	5	6	7	8
Outcome	Not completed	Not completed	Interface	GP	Spinal orthopaedics	GP	GP	Spinal orthopaedics
Comments	Patient seen for initial assessment. Given exercises, however, patient cancelled follow-up appointments	Not completed	Not completed	Not completed	Patient continued to have five further treatments of acupuncture	Not completed	Not completed	Not completed

CD, compact disc; ID, identification; N/A, not applicable.

Appendix 7 Concomitant medications reported during physiotherapy for all eight randomised participants

	Treatment group, participant ID							
	Placebo				Adalimumab			
Medication	1	2	3	4	5	6	7	8
Number of concomitant medications	1		8		7	5	10	
Medication name	• Zapain		• Omeprazole 20 mg once daily • Simvastatin 40 mg once daily • Ramipril 10 mg once daily • Venlafaxine 75 mg once daily • Temazepam 20 mg once daily • Aspirin 75 mg once daily • Metformin 500 mg once daily • Gliclazide 40 mg twice daily		• Thyroxine 25 µg once daily • Sertraline 100 mg once daily • Loestrin once daily • Omeprazole 20 mg once daily • ZOMORPH 20 mg twice daily • Diazepam 2 mg three times daily • Gabapentin 300 mg three times daily	• Gabapentin 600 mg three times daily • Paracetamol 1 g as required • Bendroflumethiazide 2.5 mg once daily • Losartan 100 mg once daily • Bezafibrate 400 mg once daily	• Zapain 30 mg four times daily • Diclofenac 50 mg three times daily • Diazepam 2 mg three times daily • Amitriptyline 10 mg once daily • Lisinopril 20 mg once daily • Lixisenatide 20 µg once daily • Felodipine 2.5 mg once daily • Gliclazide 80 mg twice daily • Metformin 850 mg twice daily • Atorvastatin 40 mg once daily	

ID, identification.

Appendix 8 Milestones

Project milestone	Completion date		Delay (months)
	Proposed	Actual	
Year 1			
Finalise protocol and trial documentation	December 2014	December 2014	0
Set up TMG	September 2014	October 2014	1
Ethics approval	December 2014	May 2015	5
R&D approval	December 2014	July 2015–August 2016	7–20
Design patient packs and CRFs	December 2014	April 2015	4
Design, validation and set-up of study database	January 2015	August 2015 (testing)	7
Randomisation set-up	February 2015	April 2015	2
DMEC and TSC meetings	November 2014	DMEC: June 2015 TSC: November 2014	DMEC: 7 TSC: 0
Physiotherapists recruited and in post	Month 1: January 2015	BCUHB: September 2015	8
		SFHT: already in post	0
		Keele: already in post	0
		Cardiff: March 2016	14
		London: December 2015	11
Set-up of centres	Month 1: January 2015	BCUHB: site opened December 2015	11
		SFHT: site opened December 2015	11
		Keele: site opened July 2016	18
		Cardiff	Not obtained before trial closed by funder
		London	Withdrew February 2016
		BCUHB: further training June, September, November 2015	5
		Keele: further training November 2015	10
		SFHT: further training July 2015	6
		Cardiff: further training January, March 2016	12
		London: further training June 2015	5
Identification of potential participants	Month 1- February 2015	BCUHB: December 2015	10
		SFHT: January 2016	11
		Keele: August 2016	18
		Cardiff	Not obtained before trial closed by funder
		London	Not applicable

Project milestone	Completion date		Delay (months)
	Proposed	Actual	
Telephone screening	Month 3: March 2015	BCUHB: December 2015	9
		SFHT: February 2016	11
		Keele: July 2016	17
		Cardiff	Not obtained before trial closed by funder
		London	Not applicable
Recruitment of participants – pilot study	Month 4: April 2015	BCUHB: March 2016	11
		SFHT: February 2016	10
		Keele	Not obtained before trial closed by funder
		Cardiff	Not obtained before trial closed by funder
		London	Not applicable
Baseline and randomisation – pilot study	Month 5: May 2015	BCUHB: March 2016	10
		SFHT: February 2016	9
		Keele	Not obtained before trial closed by funder
		Cardiff	Not obtained before trial closed by funder
		London	Not applicable
Physiotherapy clinical assessment	Month 4: April 2015	BCUHB: March 2016	11
		SFHT: March 2016	11
		Keele	Not obtained before trial closed by funder
		Cardiff	Not obtained before trial closed by funder
		London	Not applicable
Post out 6-week follow-up – pilot study	Month 7: July 2015	BCUHB: April 2016	9
		SFHT: April 2016	9
		Keele	Not obtained before trial closed by funder
		Cardiff	Not obtained before trial closed by funder
		London	Not applicable

Project milestone	Completion date		Delay (months)
	Proposed	Actual	
Year 2			
Post out 6-month follow-up	Month 10: October 2015	BCUHB: September 2016	11
		SFHT: August 2016	10
		Keele	Not obtained before trial closed by funder
		Cardiff	Not obtained before trial closed by funder
		London	Not applicable
Complete 6-month follow-up	Month 11: November 2015	BCUHB: September 2016	10
		SFHT: September 2016	10
		Keele	Not obtained before trial closed by funder
		Cardiff	Not obtained before trial closed by funder
		London	Not applicable
Post out 12-month follow-up	Month 16: April 2016	Due February 2017	Not obtained before trial closed by funder
Complete 12-month follow-up	Month 17: May 2016	Due March 2017	Not obtained before trial closed by funder
Pilot study analysis review and report	Month 11: November 2015	Eight participants recruited – November 2016	Early termination
Data cleaning and preparation for analysis	Month 10: October 2015	Eight participants recruited – November 2016	Early termination
Statistical and economic analysis	Month 20: August 2016	Eight participants recruited – November 2016	Early termination
Statistical and economic write-up	Months 4 and 37: April 2015 and January 2018	Eight participants recruited – November 2016	Early termination
Data monitoring, quality assurance and cleaning	Months 6–39: July 2015–March 2018	Trial monitored throughout set-up and during trial as per normal procedures	0
Site closure, preparation for archiving	Months 27 and 29: March 2017 and March 2018	Owing to early termination, site closure and archiving December 2016	Early termination
Year 3			
Write up of final report	Month 37: January 2018	Eight participants recruited – November 2016	Early termination
Dissemination	Month 40: April 2018	Owing to early termination, dissemination will be January 2017	Early termination

CRF, case report form; SFHT, Sherwood Forest Hospitals NHS Foundation Trust.

Appendix 9 Progress summary

Description	Timeline	Future action required	Current status
Finalisation of all documentation	Agreed by TSC and TMG: 26 January 2015	None	Complete
Approval by Bangor University Ethics Committee	9 March 2015	None	Complete
MHRA approval	15 April 2015	None	Granted/complete
REC approval	27 May 2015	None	Granted/complete
Trial closed as a result of poor recruitment	23 September 2016	Report written, sites notified and regulatory bodies notified	Ongoing

Five sites scheduled to participate in SCIATiC

Betsi Cadwaladr University Health Board: Peter Maddison Rheumatology Centre Llandudno Hospital

Description	Timeline	Future action required	Current status
R&D approval	9 July 2015	None	Complete
Contracts signed	8 April 2015	None	Complete
Research physiotherapist	15 September 2015	None	In place/complete
Site initiation	1 June 2015; further training provided on 28 September 2015 and 23 November 2015	None	Complete
Site opened to recruitment	8 December 2015	None	Complete
Participant screening	Started 8 December 2015	None	Complete
Trial participants	January 2016	Scheduled for randomisation on 18 January 2016 – participants did not attend. First participant randomised 1 March 2016, three participants recruited	Complete

Sherwood Forest Hospitals NHS Foundation Trust: Rheumatology Department, King's Mill Hospital

Description	Timeline	Future action required	Current status
R&D approval	20 November 2015	None	Granted/complete
Contracts signed	20 October 2015	None	Complete
Site initiation	28 July 2015	None	Complete
Site opened to recruitment	8 December 2015	None	Complete
Participant screening	Screening of participants in clinic started January 2016	None	Ongoing
Trial participants	March 2016	Five participants recruited	Ongoing

Bart's Health NHS Trust: The Royal London Hospital

Description	Timeline	Future action required	Current status
R&D approval	Ongoing at time of site withdrawal	None	Not applicable as site withdrew
Contracts signed	23 September 2015	None	Complete
Research physiotherapist	Ongoing at time of site withdrawal	None	Not applicable as site withdrew
Initiation performed	23 June 2015	None	Complete

Royal Wolverhampton NHS Trust: Cannock Chase Hospital and New Cross Hospital

Description	Timeline	Future action required	Current status
R&D outstanding	10 August 2016	None	Complete
Contracts outstanding	7 July 2016	None	Complete
Initiation	26 November 2015	None	Complete
Site opened to recruitment	August 2016	None	Complete
Participant screening	September 2016	One participant screened; no participants randomised before trial closure	Complete

Cardiff and Vale University Health Board

Description	Timeline	Future action required	Current status
R&D approval	Ongoing at time of early termination of trial	Final queries to be answered by site	Outstanding
Contracts	Ongoing at time of early termination of trial	In discussion with Bangor University and Cardiff and Vale University Health Board	Outstanding
Initiation	Ongoing at time of early termination of trial	Due	Outstanding

Appendix 10 Participant information sheets in English and Welsh

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Participant Information sheet

Subcutaneous Injection of Adalimumab Trial Compared with Control (SCIATiC)

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

Part 1

Introduction

We would like to invite you to take part in the SCIATiC research trial. Before deciding if you want to take part, it is important that you understand why we are doing this trial and what it will involve for you. Please take the time to read this information sheet carefully and talk to others (such as friends and family) about it if you wish.

Ask us if there is anything that you don't understand or if you need more information.

Part 1 tells you about the study and what will happen if you take part

Part 2 gives you more detailed information about how the study is conducted.

What is the purpose of the SCIATiC trial?

Sciatica is the name given to the pain caused by irritation or compression of the sciatic nerve root. The sciatic nerve runs from the back of your pelvis, through your buttocks, and all the way down both legs, ending at your feet. When a prolapsed disc irritates the sciatic nerve, it can cause pain that spreads out from your lower back and travels down your leg to your calf and often foot and toes. Sciatic pain can range from being mild to very painful. It is often associated with numbness or a pins and needles sensation.

Typical care involves the prescribing of pain relief (pain killers) or anti-inflammatory medication by your GP, and if troublesome symptoms persist, referral for physiotherapy. If pain persists patients are referred for more invasive treatment such as injections into the spine and eventually surgery. At present between 5-15% of patients with sciatica eventually need surgery.

Adalimumab is a drug given to people who suffer from inflammatory disease like rheumatoid arthritis. Adalimumab may have beneficial effects on the inflamed nerve root in sciatica. It is given by an injection under the skin in a hospital out-patient clinic.

The aim of this research is to find out how effective injections of adalimumab in conjunction with physiotherapy are, compared with an injection of saline (placebo-this a dummy treatment which looks like the real thing but is not. It contains no active ingredient) plus physiotherapy for patients with sciatica whose pain is troublesome and persistent despite treatment from their GP. 332 participants will be recruited from primary care or musculoskeletal services from five collaborating centres within the UK.

Why have I been chosen to take part?

You have been invited to take part as your sciatica persists and is troublesome despite treatment from your GP.

Do I have to take part?

No, participation in this trial is totally voluntary. If you decide to take part you will be asked to sign a consent form and be given a copy of the form to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the treatment or care that you receive in anyway.

What will I be asked to do if I decide to take part?

Your GP or a clinician from your local musculoskeletal services has looked at your medical records to see if you might be eligible, and has sent you this information sheet about the trial to ask if you are interested in taking part in this research. If you are interested in participating please either email, telephone the research team at (insert local email address), (local telephone number), or return the acceptance form in the freepost envelope provided. You will then be contacted by telephone by the research physiotherapist or a qualified member of the research team.to confirm that you are eligible and happy to continue. If so, you will be sent an appointment to attend the SCIATiC research clinic.

At the first assessment at the SCIATiC research clinic, the physiotherapist or a qualified member of the research team. will tell you all about the trial, check if you are eligible to take part and answer any questions you have about it. Should you wish to take part you will be asked to complete the consent form and will be given a copy of your consent form and this information leaflet to keep. A copy of the consent form that will be used is included with this information sheet. You will then be registered onto the trial. Three copies of the consent form will be signed, the original will be kept by the research team, the second copy will be given to you and the third copy will be filed in your medical notes.

Within two to three weeks of the first assessment visit you will be sent for a routine blood test, pregnancy urine test for women, tuberculosis (TB) screening including a chest X-ray, a research nurse will fully brief you about the adalimumab drug; and a magnetic resonance imaging (MRI) scan to exclude any serious spinal problem.

After two to three weeks from your first assessment you will need to attend a second assessment at the SCIATiC research clinic to determine if you are still eligible and confirm that all required assessments have been performed and are satisfactory. You will sign a final consent form taken by a rheumatologist, complete a questionnaire, which will take approximately 20 minutes to complete, asking about your sciatica pain and how it affects your health and then entered into the trial.

You will be given injections two weeks apart. In order to decide which injection you will receive, a computer programme will randomly allocate you to one of either the adalimumab injection group or the placebo. This means that neither you nor the research physiotherapist nor the research team know which group you are in (however, if there is a need during the trial to know then the research team can find out). In order to make a fair comparison, half of the patients taking part in the trial will receive the adalimumab injection and the other half will receive the placebo injection. You will have an equal chance of receiving adalimumab or placebo 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 you are randomised into the trial. You will also be given an appointment to return two weeks later for your 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. If your symptoms have settled after this treatment you will be referred back to your GP. If your symptoms persist then you will be referred to the spinal clinic

Follow-up questionnaires which will take approximately 20 minutes to complete will also be sent to you in the post after six weeks, six months and twelve months. They will contain a free post envelope for you to return them. You will receive message alerts prior to questionnaires being sent out and regular newsletters notifying you when questionnaires have been sent. Two weeks after the last questionnaire has been sent you will be contacted by a member of the research team. They will ask you about your overall experience of the trial and follow-up treatment as well as asking which treatment group you think you were in.

Will I be reimbursed for participating in the trial?

You can claim back your travel expenses for getting to and from the hospital (please keep your receipts or tickets, and show them to the study research team).

What are the drugs being tested?

Adalimumab has been prescribed in the UK for a number of years to people who suffer from inflammatory disease like rheumatoid arthritis. It is one of the groups of drugs known as monoclonal antibodies (MAB); MABs are a type of biological therapy. Adalimumab may have beneficial effects on the inflamed nerve root in sciatica as it is an anti-TNF drugs which block the action of TNF and so reduce this inflammation. It is given by an injection under the skin in a hospital out-patient clinic.

What are the alternatives?

Physiotherapy is usually considered normal practice for those participants that fail to improve with GP care.

What are the possible disadvantages and risks of taking part?

The trial generally follows the normal physiotherapy treatment but with some newer treatments added to see if they are of benefit. You should not be disadvantaged by entering the study. However, you will need to attend the research clinic at the following time points:-

- First assessment - check eligibility, if found to be eligible initial consent and registered onto the trial. Sent for routine bloods, Urine pregnancy test if female, TB testing and biological counselling about the drug, MRI.
- Second assessment – results of blood test, TB testing and MRI checked to confirm eligibility, final consent form completed, baseline questionnaire completed, allocated to treatment group at random. You will receive the first injection at this visit.
- Third Assessment – The second injection will be given.

You will also be referred for physiotherapy at your local physiotherapy department. This will be up to six treatments over a period of twelve weeks 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. Your physiotherapy treatment should preferably start at the same week as your first injection. You will not receive any other NHS-based co-intervention until this physiotherapy treatment has finished.

Adalimumab has known side-effects. These will be discussed with you at the start of the trial by the rheumatology specialist nurse, 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 you may be more likely to develop infections. At the same time, adalimumab can mask the symptoms of infection so you may not feel as ill as you normally would when you do have an infection.

You should tell your research physiotherapist or rheumatology specialist nurse straight away if you develop any of the following after starting adalimumab:

- a sore throat
- a fever
- any other symptoms of infection
- any other new symptoms or anything else that concerns you.

In order to use it safely, participants will receive screening for TB and counselling about its effects from nurses experienced in its use. Part of the TB testing is to undergo as chest x-ray. X-rays are a type of radiation known as ionising radiation. The dose that you get from a medical x-ray is very low and the associated risks are minimal. They are similar in strength to other sources of natural radiation that people are exposed to everyday without even realising it. The radiographer is responsible for making sure that your dose is kept as low as possible and that the benefits of having the x-ray outweigh any risk. You will also undergo an MRI. This is a very safe procedure for most patients. However, patients with heart pacemakers and certain other surgical implants, for example a cochlear implant, cannot be scanned. You will be asked to complete and sign a safety questionnaire before your scan to make sure it is safe for you to be scanned.

If you are, or think you may be pregnant you must tell a member of staff in the radiology department knows as soon as possible. The radiation in an X-ray can be harmful for an unborn baby and MRI scans are not advisable in early pregnancy unless there are special circumstance

Like all drugs the adalimumab may have side-effects that we don't know about yet. This is unlikely because it is being used to treat patients throughout the NHS. However, you should report anything out of the ordinary or that may concern you to the research physiotherapist or rheumatology specialist nurse in case it represents a potential side-effect. All side-effects are reported to the study organisers in Bangor University who will keep a very close watch on any problems that might develop. Similarly, all effects and benefits are confidentially reviewed by an independent group of doctors who are not involved with the study at all. This is to ensure that any problems are rapidly identified and acted upon.

It is important that women of child-bearing age do not become pregnant while on this trial as the effects of these treatments on the foetus are unknown. Pregnant women must not take part in this study, and women should not plan to become pregnant during the study. A urine pregnancy test will be performed as part of the screening assessment to exclude the possibility of pregnancy. Women who could become pregnant must use an effective

contraceptive during the course of this study or for a safety period of five months after the last injection. Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor.
It is not known if the study medicine will affect sperm or semen and therefore you should not father a child during this study or for a safety period of five months after the last injection.
If your partner might become pregnant you must use reliable forms of contraception during the trial and for five months afterwards. If your partner becomes pregnant during the study or within five months of stopping treatment, you should inform your study doctor immediately.
Should you or your partner fall pregnant during the trial the need for additional medical supervision will be discussed with you.

What are the possible benefits of taking part?

You will receive physiotherapy treatment in addition to the injections, for your 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 you will benefit from the physiotherapy treatment. We do not know whether you will benefit from the injections, but we hope that the information we get from the trial results will help to improve the treatment option for patients with sciatica

What else should I know about adalimumab?

It is recommended that you carry a biological therapy alert card, which you can get from your doctor or rheumatology nurse. Then if you become unwell, anyone treating you will know that you're on the SCIATiC trial and that you are therefore at risk of its side-effects, including infections.

Can I take other medicines alongside adalimumab?

Adalimumab may be prescribed alongside other drugs. You should discuss any new medications with your doctor before starting them, and you should always tell any other doctor treating you that you are on adalimumab. You should also be aware of the following points:

- Adalimumab is not a painkiller. If you are already on painkillers or anti-inflammatory medication you can carry on taking these as well as adalimumab, unless your doctor

advises otherwise. If adalimumab works for you, you may be able to reduce painkillers or anti-inflammatory after a time.

- Do not take over-the-counter preparations or herbal remedies without discussing this first with your research physiotherapist, rheumatology nurse or pharmacist.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to one of your local study team or to the trial organisers. The Chief Investigator for the whole study is Dr Nefyn Williams. The principal investigator for the North Wales centre is Professor Clare Wilkinson. If you think you have suffered harm or negligence, you may complain through your local hospital complaints procedure or you may have grounds for a legal action against the trial sponsor which is Bangor University.
Detailed information about this is given in Part 2.

Will my taking part in this study be kept confidential?

All information collected in this study will be kept strictly confidential. Only members of the research team will have access to it. Each person who consents to take part in the trial will be given a unique code number so no names or details identifying specific individuals will be used on questionnaires or included in any study reports. This means that the data is anonymous. If you consent to take part in the research, your medical records may be inspected by the hospital personnel or the Chief Investigator or his nominee on behalf of the trial Sponsor who is Bangor University for purposes of analysing the results. Your GP will be informed, with your consent that you wish to take part in a clinical study

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This completes Part 1. If you are interested in the study, please read the additional information in Part 2 before making any decision.

Please insert local header

Patient Information

Subcutaneous Injection of Adalimumab Trial Compared with Control (SCIATiC)

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

Part 2

What if new information becomes available?

As the study progresses, new information about the treatments or results may become available. If this happens, we will tell you and discuss what it means for you. It may mean that you should withdraw from the study and your doctor will explain this if need be. Your doctor will continue your treatment using the best treatments available.

What will happen if I don't want to carry on with the study?

If you decide not to continue the trial for any reason, you should discuss this with your doctor. You are free to withdraw at any time, but it is best to let your doctor know so that they can make the best arrangements to ensure the treatment of your sciatica continues in the best way possible. If you withdraw, we will still need to use the information we have

collected about the treatment you were given and how well you did, up to the time you withdraw. You can also withdraw from the trial, but still allow us to tell the study organisers from time to time how well you are doing.

What happens if something goes wrong?

We believe that this study is safe and we do not expect you to suffer any harm or injury because of your participation in it. The NHS indemnity scheme will compensate you if you are harmed due to someone's negligence but there is no compensation scheme for harm that was not caused by negligence. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during this study, the normal National Health Service complaints mechanisms will be available to you. However, we would ask you first to speak to one of the research team, so that we can try to address your concerns and find a solution. You can talk to the local researcher (*insert local contact details*) or you can contact the Chief Investigator, Dr Nefyn Williams (contact details removed Telephone: Contact details removed E-mail: Contact details removed If you are not satisfied with our response you can make a complaint to the trial sponsor which is Bangor University Mrs Gwenan Hine, contact details removed tel Contact details removed

What will happen to the results of the research study?

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. In addition to preparing an article 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 National Institute for Health and Care Excellence (NICE). 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, for example 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.

Who is organising and funding the research?

We have obtained a grant from the National Institute for Health Research. The Chief Investigator is Dr Nefyn Williams from Bangor University and his team includes researchers, doctors and other health professionals from Bangor University and the Betsi Cadwaladr University Health Board. The Lead Investigator for the North Wales centre is Professor Clare Wilkinson.

What should I do if I have any concerns about the study?

If you have any concerns about the study, please contact the Chief Investigator in the first instance.

Dr Nefyn Williams
Chief Investigator, SCIATiC

Dr Clare Wilkinson
Lead Investigator, SCIATiC

There is also a lead person at your local institution. In the case of (CENTRE), that is (PERSON) who can be contacted on (TELEPHONE)

What do I do now?

If you agree to take part in the study a research physiotherapist or a qualified member of the research team will be contacting you to see if you might be eligible, and if you are, will give you an appointment to see you in a research clinic

This completes Part 2. If you have any further questions, please ask a member of your local study team. If you are happy to take part in the study, you team will ask you to complete the attached consent form. You will be able to keep a copy of this.

Thank you

Please keep this information sheet for your records

If you agree to enter the study.

Nodwch bennyn lleol

Taflen Wybodaeth i Gyfranogwyr

Treial Pigiad Isgroenol o Adalimumab o'i Gymharu â Rheolydd (SCIATiC)

Treial dan reolaeth ar hap o bigiad adalimumab o'i gymharu â phlasebo ar gyfer cleifion sy'n cael triniaeth ffisiotherapi ar gyfer clunwst

Rhan 1

Cyflwyniad

Hoffem eich gwahodd i gymryd rhan yn nhreial astudiaeth SCIATiC. Cyn penderfynu a ddymunwch gymryd rhan, mae'n bwysig eich bod yn deall pam ein bod yn cynnal y treial hwn a beth fydd yn ei olygu i chi. Rhowch o'ch amser i ddarllen y daflen wybodaeth hon yn ofalus a siaradwch â phobl eraill (fel teulu a ffrindiau) amdano os dymunwch.

Gofynnwch i ni os oes unrhyw beth nad ydych yn ei ddeall neu os oes angen mwy o wybodaeth arnoch.

Mae Rhan 1 yn dweud wrthych am yr astudiaeth a beth fydd yn digwydd os byddwch yn cymryd rhan

Mae Rhan 2 yn rhoi gwybodaeth fwy manwl i chi am sut fydd yr astudiaeth yn cael ei chynnal.

Beth yw diben y treial SCIATiC?

Clunwst (sciatica) yw'r enw a roddir i'r boen a achosir gan lid neu gywasgiad gwreiddyn y nerf siatig. Mae'r nerf siatig yn rhedeg o gefn eich pelfis, trwy eich ffolennau, a'r holl ffordd i lawr y ddau goes, gan orffen yn eich traed. Pan fydd disg wedi llithro o'i le yn llidio'r nerf siatig, gall achosi poen sy'n lledaenu o ran isaf eich cefn ac yn teithio i lawr eich coes i'ch croth coes ac yn aml i'ch troed a bysedd y troed. Gall poen siatig amrywio o ysgafn i boenus iawn. Yn aml mae'n gysylltiedig â fferdod neu deimlad pinnau bach.

Mae gofal nodweddiadol yn golygu cyffuriau lleddfu poen neu feddyginiaeth wrthlidiol ar bresgripsiwn gan eich Meddyg Teulu, ac os bydd symptomau trafferthus yn parhau, atgyfeiriad ar gyfer ffisiotherapi. Os bydd poen yn parhau, bydd cleifion yn cael eu hatgyfeirio ar gyfer triniaeth mwy mewnwthiol fel pigiadau i'r asgwrn cefn a llawdriniaeth yn y pen draw. Ar hyn o bryd, mae 5-15% o gleifion â chlunwst angen llawdriniaeth yn y pen draw.

Cyffur yw adalimumab sy'n cael ei roi i bobl sy'n dioddef gan glefyd llidiol fel arthritis gwynegol. Efallai bod adalimumab yn cael effeithiau buddiol ar wreiddyn y nerf llidiol mewn clunwst. Mae'n cael ei roi trwy bigiad o dan y croen mewn clinig cleifion allanol mewn ysbyty.

Nod yr ymchwil hwn yw darganfod pa mor effeithiol y mae pigiadau adalimumab ar y cyd â ffisiotherapi, o'u cymharu â phigiad o doddiant halwyn (plasebo - dyma driniaeth ffug sy'n edrych fel y driniaeth go iawn ond nid dyma ydyw. Nid yw'n cynnwys unrhyw gynhwysyn gweithredol) yn ogystal â ffisiotherapi i gleifion â chlunwst â phoen sy'n drafferthus er gwaethaf triniaeth eu meddyg teulu. Bydd 332 o gyfranogwyr yn cael eu recriwtio o wasanaethau gofal sylfaenol neu gyhyrysgerbydol o bum canolfan sy'n cydweithredu yn y DU.

Pam ydw i wedi cael fy newis i gymryd rhan?

Rydych chi wedi cael eich dewis i gymryd rhan oherwydd bod eich clunwst yn parhau ac mae'n drafferthus er gwaethaf triniaeth eich meddyg teulu.

A oes yn rhaid i mi gymryd rhan?

Nac oes, mae cyfranogiad yn y treial hwn yn hollol wirfoddol. Os penderfynwch gymryd rhan bydd gofyn i chi lofnodi ffurflen gydsyniad a byddwch yn cael copi o'r ffurflen i'w gadw. Os byddwch yn penderfynu cymryd rhan byddwch yn dal i fod yn rhydd i dynnu'n ôl ar unrhyw adeg a heb roi rheswm. Os byddwch yn penderfynu tynnu'n ôl ar unrhyw adeg, neu'n

penderfynu peidio â chymryd rhan, ni fydd hynny'n effeithio ar eich triniaeth neu ofal mewn unrhyw ffordd.

Beth fydd gofyn i mi wneud os byddaf yn penderfynu cymryd rhan?

Mae eich meddyg teulu neu glinygydd o'ch gwasanaethau cyhyrysgerbydol lleol wedi edrych ar eich cofnodion meddygol i weld a allech fod yn gymwys, ac wedi anfon y daflen wybodaeth hon atoch ynglŷn â'r treial i ofyn a oes gennych ddiddordeb mewn cymryd rhan yn yr ymchwil hwn. Os oes gennych ddiddordeb mewn cymryd rhan, e-bostiwch, ffoniwch y tîm ymchwil yn (nodwch gyfeiriad e-bost lleol), (rhif ffôn lleol), neu dychwelwch y ffurflen dderbyn yn yr amlen rhadbost a ddarparwyd. Yna bydd y ffisiotherapydd ymchwil neu aelod cymwysedig o'r tîm ymchwil yn cysylltu â chi dros y ffôn i gadarnhau eich bod yn gymwys ac yn hapus i barhau. Os felly, bydd apwyntiad yn cael ei anfon atoch i fynychu clinig ymchwil SCIATiC.

Yn yr asesiad cyntaf yng nghlinig ymchwil SCIATiC, bydd y ffisiotherapydd neu aelod cymwysedig o'r tîm ymchwil yn dweud popeth wrthych am y treial, yn gwirio a ydych yn gymwys i gymryd rhan ac yn ateb unrhyw gwestiynau a allai fod gennych amdano. Os dymunwch gymryd rhan bydd gofyn i chi gwblhau'r ffurflen gydsyniad a byddwch yn cael copi o'ch ffurflen gydsyniad a'r daflen wybodaeth hon i'w cadw. Mae copi o'r ffurflen gydsyniad a ddefnyddir wedi'i gynnwys â'r daflen wybodaeth hon. Yna byddwch wedi cofrestru ar y treial. Bydd tri chopi o'r ffurflen gydsyniad yn cael eu llofnodi, bydd y tîm ymchwil yn cadw'r copi gwreiddiol, byddwch chi'n cael yr ail gopi a bydd y trydydd copi'n cael ei ffeilio yn eich nodiadau meddygol.

Cyn pen dwy neu dair wythnos o'r ymweliad asesu cyntaf byddwch yn cael eich anfon am brawf gwaed fel mater o drefn, prawf wrin beichiogrwydd i ferched, sgrinio twbercwlosis (TB) gan gynnwys pelydr-X o'r frest, bydd nyrs ymchwil yn darparu gwybodaeth lawn i chi am y cyffur adalimumab; a sgan delweddu atseiniol magnetig (MRI) i sicrhau nad oes unrhyw broblemau sbinol difrifol.

Dwy neu dair wythnos ar ôl eich asesiad cyntaf bydd angen i chi fynychu ail asesiad yng nghlinig ymchwil SCIATiC i bennu a ydych yn parhau i fod yn gymwys a chadarnhau bod yr holl asesiadau gofynnol wedi cael eu cynnal ac yn foddhaol. Bydd angen i chi lofnodi ffurflen gydsyniad terfynol wedi'i chymryd gan riwmatolegydd, llenwi holiadur, y bydd yn cymryd oddeutu 20 munud i'w lenwi, gofyn am eich poen clunwst a sut mae'n effeithio ar eich iechyd ac yna byddwch yn ymuno â'r treial.

Byddwch yn cael pigiadau â phythefnos rhyngddynt. Er mwyn penderfynu pa bigiad byddwch yn ei gael, bydd rhaglen gyfrifiadur yn eich dyrannu ar hap i naill a'r grŵp pigiad

adalimumab ynteu'r grŵp plasebo. Mae hyn yn golygu na fyddwch chi na'r ffisiotherapydd ymchwil a'r tîm ymchwil yn gwybod i ba grŵp rydych yn perthyn (fodd bynnag, os bydd angen darganfod hyn yn ystod y treial, yna gall y tîm ymchwil ddarganfod hyn). Er mwyn gwneud cymhariaeth deg, bydd hanner y cleifion sy'n cymryd rhan yn y treial yn cael y pigiad adalimumab a bydd yr hanner arall yn cael y pigiad plasebo. Bydd gennych siawns cyfartal o gael pigiadau adalimumab neu doddiant halwyn plasebo (plasebo). Bydd rhiwmatolegydd ymgynghorol yn rhoi'r pigiadau ar bresgripsiwn a bydd nyrs arbenigol rhiwmatoleg sy'n brofiadol o ran rhoi'r pigiadau hyn yn eu rhoi. Byddwch yn cael y pigiadau cyntaf ar yr un diwrnod ag y byddwch yn ymuno â'r treial ar hap. Hefyd byddwch yn cael apwyntiad i ddychwelyd pythefnos yn ddiweddaraf ar gyfer eich pigiad olaf. Bydd y ddau grŵp hefyd yn mynychu cwrs o ffisiotherapi a fydd yn cynnwys pecyn o driniaeth sy'n cynnwys ymarferion corff a ddyluniwyd i gleifion â chlunwst. Os bydd eich symptomau wedi gwella ar ôl y driniaeth hon byddwch yn cael ei atgyfeirio'n ôl i'ch meddyg teulu. Os bydd eich symptomau'n parhau yna byddwch yn cael ei atgyfeirio i'r clinig sbinol

Hefyd bydd holiaduron dilynol, a fydd yn cymryd oddeutu 20 munud i'w llenwi, yn cael eu hanfon atoch yn y post ar ôl chwe wythnos, chwe mis a deuddeg mis. Byddant yn cynnwys amlen rhadbost er mwyn i chi eu dychwelyd. Byddwch yn cael negeseuon rhybuddio cyn i holiaduron gael eu hanfon atoch a chylchlythyrau rheolaidd yn rhoi gwybod i chi pan fydd holiaduron wedi cael eu hanfon. Bythefnos ar ôl i'r holiadur olaf gael ei anfon bydd aelod o'r tîm ymchwil yn cysylltu â chi. Bydd ef/hi'n gofyn i chi am eich profiad cyffredinol o'r treial a thriniaeth ddilynol yn ogystal â gofyn i ba grŵp triniaeth ydych chi'n meddwl eich bod yn perthyn.

A fyddaf yn cael fy ad-dalu am gymryd rhan yn y treial?

Gallwch ad-hawlio eich costau teithio am gyrraedd yr ysbyty a mynd yn ôl adref (cadwch eich derbynebau neu docynnau, a dangoswch y rhain i dîm ymchwil yr astudiaeth).

Pa gyffuriau sy'n cael eu rhoi ar brawf?

Mae adalimumab wedi cael ei roi ar bresgripsiwn ers nifer o flynyddoedd i bobl sy'n dioddef gan glefyd llidiol fel arthritis gwynegol. Mae'r perthyn i'r grwpiau o gyffuriau o'r enw gwrthgyrff monoclonaidd (MAB); mae MABs yn fath o therapi biolegol. Efallai y bydd adalimumab yn cael effeithiau buddiol ar wreiddyn y nerf sy'n llidiol mewn clunwst oherwydd ei fod yn gyffur gwrth-TNF sy'n rhwystro gweithrediad TNF ac felly'n lleihau'r llid hwn. Mae'n cael ei roi trwy bigiad o dan y croen mewn clinig cleifion allanol mewn ysbyty.

Beth yw'r dewisiadau amgen?

Fel arfer ystyrir ffisiotherapi fel ymarfer normal ar gyfer y cyfranogwyr hynny sy'n methu â gwella â gofal meddyg teulu.

Beth yw anfanteision a risgiau posibl cymryd rhan?

Yn gyffredinol mae'r treial yn dilyn y driniaeth ffisiotherapi normal ond â rhai triniaethau mwy newydd wedi'u hychwanegu i weld a ydynt o fudd. Ni ddylech fod o dan anfantais trwy ymuno â'r astudiaeth. Fodd bynnag, bydd angen i chi fynychu'r clinig ymchwil ar y pwyntiau amser canlynol:-

- Asesiad pellach - gwirio cymhwysedd, os darganfyddir eich bod yn gymwys, cydsyniad cychwynnol a chofrestru ar y treial. Anfon am brofiad gwaed fel mater o drefn, Prawf wrin beichiogrwydd os yn fenywaidd, profion TB a chwnsela ynglŷn â'r cyffur, MRI.
- Ail asesiad - canlyniadau prawf gwaed, profion TB a gwirio MRI i gadarnhau cymhwysedd, llenwi ffurflen gydsyniad terfynol, llenwi holiadur gwaelodlin, dyrannu i grŵp triniaeth ar hap. Byddwch yn derbyn y pigiad cyntaf yn yr ymweliad hwn.
- Trydydd Asesiad - Bydd yr ail bigiad yn cael ei roi.

Byddwch hefyd yn cael eich atgyfeirio ar gyfer ffisiotherapi yn eich adran ffisiotherapi leol. Bydd hyd at chwe thriniaeth dros gyfnod deuddeg wythnos wedi'i bennu gan ddewisiadau'r cyfranogwr a'r therapydd yn ogystal â'r ymateb i driniaeth. Byddwn yn casglu ac yn disgrifio'r agweddau hyn ar driniaeth ffisiotherapi fel rhan o'r treial. Yn ddelfrydol dylai'ch triniaeth ffisiotherapi ddechrau yn yr un wythnos â'ch pigiad cyntaf. Ni fyddwch yn derbyn unrhyw gyd-ymyrraeth arall gan y GIG nes bod y driniaeth ffisiotherapi hon wedi gorffen.

Mae gan adalimumab sgil-effeithiau hysbys. Bydd y nyrs arbenigol rhiwmatoleg yn trafod y rhain â chi ar ddechrau'r treial, ond mae gennym lawer o brofiad o'i ddefnyddio'n ddiogel ar gyfer afiechydon fel arthritis gwynegol. Y sgil-effeithiau mwyaf cyffredin yw adweithiau yn safle'r pigiad, fel cochni, chwydd neu boen. Fel arfer nid yw'r adweithiau hyn yn ddifrifol.

Mae adalimumab yn effeithio ar y system imiwnedd (system amddiffyn y corff), felly efallai y byddwch yn fwy tebygol o ddatblygu heintiau. Ar yr un adeg, gall adalimumab guddio symptomau haint fel efallai na fyddwch yn teimlo mor sâl ag y byddech fel arfer pan fydd gennych haint.

Dylech ddweud wrth eich ffisiotherapydd ymchwil neu nyrs arbenigol rhiwmatoleg ar unwaith os byddwch yn datblygu unrhyw un neu rai o'r symptomau canlynol ar ôl dechrau ar adalimumab:

- dolur gwddf
- twymyn
- unrhyw symptom arall o haint
- unrhyw symptomau eraill newydd neu unrhyw beth arall sy'n achos pryder i chi.

Er mwyn ei ddefnyddio yn ddiogel, bydd cyfranogwyr yn cael eu sgrinio ar gyfer TB a'u cwnsela am ei effeithiau gan nyrsys sy'n brofiadol yn ei ddefnydd. Rhan o'r profion TB yw ymgymryd â phelydr-x o'r frest. Math o ymbelydredd yw pelydr-x sy'n cael ei alw'n ymbelydredd ïoneiddio. Bydd y dos a gewch o belydr-x meddygol yn isel iawn ac mae'r risgiau sy'n gysylltiedig â hyn yn fach iawn. Maent yn debyg o ran cryfder i ffynonellau eraill o ymbelydredd naturiol bydd pobl yn agored iddynt bob dydd heb hyd yn oed sylweddoli. Mae'r radiograffydd yn gyfrifol am wneud yn siŵr bod y dos yn cael ei gadw mor isel â phosibl a bod buddion cael y pelydr-x yn gorbwyso unrhyw risg. Byddwch hefyd yn cael MRI. Dyma weithred ddiogel iawn i'r rhan fwyaf o gleifion. Fodd bynnag, ni fydd cleifion â rheolyddion calon a rhai mathau eraill o fewnblaniadau llawfeddygol, er enghraifft, mewnblaniad cochleaidd, yn gallu cael eu sganio. Bydd gofyn i chi lenwi a llofnodi holiadur diogelwch cyn eich sgan i wneud yn siŵr ei bod yn ddiogel i chi gael eich sganio.

Os ydych chi'n feichiog, neu'n meddwl y gallech fod yn feichiog, mae'n rhaid i chi roi gwybod i aelod o staff yn yr adran radioleg cyn gynted â phosibl. Gall yr ymbelydredd mewn pelydr-X fod yn niweidiol i fabi yn y groth ac ni chynghori sganiau MRI yn ystod beichiogrwydd cynnar oni bai bod amgylchiadau arbennig

Fel pob cyffur, efallai y bydd adalimumab yn achosi sgil-effeithiau nad ydynt eto'n hysbys i ni. Mae hyn annhebygol oherwydd ei fod yn cael ei ddefnyddio i drin cleifion yn y GIG drwyddo draw. Fodd bynnag, dylech roi gwybod i ffisiotherapydd yr ymchwil neu'r nyrs arbenigol rhiwmatoleg am unrhyw beth anarferol neu unrhyw beth a allai achosi pryder i chi, rhag ofn ei fod yn cynrychioli sgil-effaith bosibl. Adroddir i drefnwyr yr ymchwil ym Mhrifysgol Bangor am bob sgil-effaith, a byddant yn cadw golwg agos iawn ar unrhyw broblemau a allai ddatblygu. Yn debyg, bydd yr holl effeithiau a buddion yn cael eu hadolygu yn gyfrinachol gan grŵp annibynnol o feddygon nad ydynt yn gysylltiedig â'r astudiaeth. Nod hyn yw sicrhau bod unrhyw broblemau'n cael eu nodi'n gyflym a gweithredir arnynt yn gyflym.

Mae'n bwysig na fydd merched o oedran cario plant yn dod yn feichiog tra byddant yn rhan o'r treial hwn oherwydd bod effeithiau'r triniaethau hyn ar y ffetws yn anhysbys. Ni chaniateir i ferched beichiog gymryd rhan yn yr astudiaeth hon, ac ni ddylai merched gynllunio dod yn feichiog yn ystod yr astudiaeth. Bydd prawf wrin beichiogrwydd yn cael ei gynnal fel rhan o'r asesiad sgrinio i sicrhau nad oes posibilrwydd o feichiogrwydd. Mae'n rhaid i ferched a allai ddod yn feichiog ddefnyddio dull atal cenhedlu effeithiol yn ystod yr astudiaeth hon neu am

gyfnod diogelwch o bum mis ar ôl y pigiad olaf. Dylai unrhyw ferch sy'n darganfod ei bod yn feichiog wrth gymryd rhan yn yr astudiaeth roi gwybod ar unwaith i'w meddyg ymchwil.
Nid yw'n hysbys a fydd meddyginiaeth yr astudiaeth yn effeithio ar sberm neu semen ac felly ni ddylech genhedlu plentyn yn ystod yr astudiaeth hon neu am gyfnod diogelwch o bum mis ar ôl y pigiad olaf.
Os gallai'ch partner ddod yn feichiog mae'n rhaid i chi ddefnyddio ffurfiau dibynadwy o atal cenhedlu yn ystod y treial ac am bum mis wedyn. Os bydd eich partner yn dod yn feichiog yn ystod yr astudiaeth neu o fewn pum mis i roi'r gorau i driniaeth, dylech roi gwybod i'ch meddyg astudiaeth ar unwaith. Os byddwch chi neu'ch partner yn dod yn feichiog yn ystod y treial, bydd yr angen am oruchwyliaeth feddygol ychwanegol yn cael ei thrafod â chi.

Beth ydi buddion posibl cymryd rhan?

Byddwch yn derbyn triniaeth ffisiotherapi yn ogystal â'r pigiadau, ar gyfer eich poen sciatig. Yn aml bydd ffisiotherapi'n cael ei ddefnyddio ar gyfer cleifion â chlunwst a cheir tystiolaeth i awgrymu ei fod yn helpu nifer ohonynt. Rydym yn gobeithio y byddwch yn cael budd o'r driniaeth ffisiotherapi. Nid ydym yn gwybod a fyddwch yn cael budd o'r pigiadau, ond rydym yn gobeithio y bydd y wybodaeth a gawn trwy ganlyniadau'r treial yn helpu i wella'r opsiwn triniaeth ar gyfer cleifion â chlunwst

Beth arall dylwn i wybod am adalimumab?

Argymhellir eich bod yn cludo cerdyn rhybudd therapi biolegol, a gallwch gael un o'r rhaid oddi wrth eich meddyg neu nyrs rhiwmatoleg. Yna os byddwch yn teimlo'n sâl, bydd unrhyw un sy'n eich trin yn gwybod eich bod ar y treial SCIATiC ac felly eich bod mewn perygl o'i sgil-effeithiau, gan gynnwys heintiau.

Alla i gymryd meddyginiaethau eraill ochr wrth ochr ag adalimumab?

Gellir rhoi adalimumab ar bresgripsiwn ochr wrth ochr â chyffuriau eraill. Dylech drafod unrhyw feddyginiaethau newydd â'ch meddyg cyn cychwyn arnynt, a dylech bob amser rhoi gwybod i unrhyw feddyg arall sy'n eich trin eich bod ar adalimumab. Dylech hefyd fod yn ymwybodol o'r pwyntiau canlynol:

- Nid cyffur lleddfu poen mo adalimumab. Os ydych eisoes yn cymryd cyffuriau lleddfu poen neu feddyginiaeth wrthlidiol, gallwch barhau i gymryd y rhain yn ogystal ag adalimumab, oni bai bod eich meddyg yn rhoi cyngor gwahanol. Os bydd

adalimumab yn gweithio i chi, efallai y byddwch yn gallu lleihau cyffuriau lleddfu poen neu wrthlidiol ar ôl cyfnod.

- Peidiwch â chymryd paratoadau dros y cownter neu feddyginiaethau llysieuol heb drafod hyn yn gyntaf â'ch ffisiotherapydd ymchwil, nyrs rhiwmatoleg neu fferyllydd.

Beth os bydd yna broblem?

Os oes gennych bryder ynglŷn ag unrhyw agwedd ar yr astudiaeth hon, dylech siarad ag un o'ch tîm astudiaeth lleol neu â threfnwyr y treial. Prif Ymchwilydd yr holl astudiaeth yw Dr Nefyn Williams. Prif Ymchwilydd canolfan Gogledd Cymru yw'r Athro Clare Wilkinson. Os credwch eich bod wedi dioddef niwed neu esgeulustod, gallwch gwyno trwy weithdrefn gwyno eich ysbyty lleol neu efallai y bydd gennych sail i ddwyn achos cyfreithiol yn erbyn noddwr y treial sef Prifysgol Bangor.
Rhoddir gwybodaeth fanwl am hyn yn Rhan 2.

A fydd y ffaith fy mod yn cymryd rhan yn yr astudiaeth hon yn cael ei chadw yn gyfrinachol?

Bydd yr holl wybodaeth a gesglir yn yr astudiaeth hon yn cael ei chadw'n hollol gyfrinachol. Aelodau o'r tîm ymchwil yn unig fydd yn cael mynediad ati. Bydd pob unigolyn sy'n rhoi cydsyniad i gymryd rhan yn y treial yn cael cod unigryw felly ni fydd unrhyw enwau neu fanylion sy'n galluogi adnabod unigolion penodol yn cael eu defnyddio ar holiaduron neu'n cael eu cynnwys mewn unrhyw adroddiadau astudiaeth. Mae hyn yn golygu bod y data yn ddienw. Os byddwch yn rhoi cydsyniad i gymryd rhan yn yr ymchwil, efallai y bydd personél yr ysbyty neu'r Prif Ymchwilydd neu ei enwebai, yn archwilio eich cofnodion meddygol ar ran Noddwr y treial sef Prifysgol Bangor at ddibenion dadansoddi'r canlyniadau. Rhoddir gwybod i'ch meddyg teulu, â'ch cydsyniad eich bod yn dymuno cymryd rhan mewn astudiaeth glinigol

Mae hyn yn cwblhau Rhan 1. Os oes gennych ddiddordeb yn yr astudiaeth, darllenwch y wybodaeth ychwanegol yn Rhan 2 cyn gwneud unrhyw benderfyniad.

Appendix 11 Consent forms in English and Welsh

Please print on locally headed paper

Patient Informed Consent Form for Registration to:-

A randomised 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)

Name of Researcher:……..

Participant Identification Number:…….

Please initial

Each box

1. I confirm that I have read and understand the participant information sheet part 1 dated Sheet Version 3 dated 16th March 2016 for this study and I have had the opportunity to ask questions about the study ☐

2. I understand that I am consenting to register to the SCIATiC study and my participation is voluntary and that I am free to withdraw at any time, without giving any reason. I understand that if I withdraw this will not affect my healthcare or legal rights in any way. If I withdraw from the study the researchers will use the information I have provided up to that point, unless I indicate that I do not want them to. ☐

3. I understand that the information I give to the researchers will only be used for the purposes of research, and that personal details will be treated in the strictest confidence ☐

4. I have spoken with Dr / Mr. /Ms. _____ ☐

5. I understand that I am free to withdraw from the study: ☐

   - at any time
   - without having to give reasons
   - without affecting my future medical care

6. I understand sections of my medical notes will be accessed and used by individuals involved in the trial or from regulatory authorities where it is relevant to my taking part in the research. I give my permission for these individuals to have access to my NHS records, including hospital notes, GP notes and physiotherapy notes, and for details from these records to be linked to the trial data to provide additional information to support the research. All personal details will be treated as STRICTLY CONFIDENTIAL. The information will be used for medical research only and I will be identified only by trial number, initials and date of birth. I will not be identified in any way in analysis and reporting of the results. ☐

7. I give permission to tell my GP about my participation in the study ☐

8. I agree to be registered into the study ☐

Patient's Signature: _____

Name in block letters: _____

Date: _____

Research Physiotherapist or Doctor's Signature: _____

Research Physiotherapist or Doctor's name in block letters: _____

Date: _____

Patient's Representative's signature (if appropriate): _____

Representative's name in block letters: _____

SCIATIC

SubCutaneous
Injection of
Adalimumab
Trial Compared
with
Control

Representative's relationship to patient: _____

Date: _____

When completed please give a copy to the participant; a copy for the researcher site file; and file the original in the participants' medical note.

Please print on locally headed paper

Patient Informed Consent Form for Randomisation to:

A randomised 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)

Name of Researcher:……..

.Participant Identification Number:…….

Please initial

1. I confirm that I have read and understand the participant information sheet dated Sheet Version 3 dated 16h March 2016 for this study and I have had the opportunity to ask questions about the study ☐

2. I understand that I am consenting to be randomised to the SCIATiC study that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. I understand that if I withdraw this will not affect my healthcare or legal rights in any way. If I withdraw from the study the researchers will use the information I have provided up to that point, unless I indicate that I do not want them to. ☐

3. I understand that the information I give to the researchers will only be used for the purposes of research, and that personal details will be treated in the strictest confidence ☐

4. I have spoken with Dr / Mr. /Ms. _____ ☐

5. I understand that I am free to withdraw from the study: ☐

   - at any time
   - without having to give reasons
   - without affecting my future medical care

6. I understand sections of my medical notes will be accessed and used by individuals involved in the trial or from regulatory authorities where it is relevant to my taking part in the research. I give my permission for these individuals to have access to my NHS records, including hospital notes, GP notes and physiotherapy notes, and for details from these records to be linked to the trial data to provide additional information to support the research. All personal details will be treated as STRICTLY CONFIDENTIAL. The information will be used for medical research only and I will be identified only by trial number, initials and date of birth. I will not be identified in any way in analysis and reporting of the results. ☐

7. I give permission to tell my GP about my participation in the study ☐

8. I agree to participate in the study ☐

9 I agree to be randomised into the SCIATiC study ☐

Patient's Signature: _____

Name in block letters: _____

Date: _____

Doctor's Signature: _____

Doctor's name in block letters: _____

Date: _____

Patient's Representative's signature _____

(if appropriate):

Representative's name in block letters: _____

Representative's relationship to patient: _____

Date: _____

When completed please give a copy to the participant; a copy for the researcher site file; and file the original in the participants' medical notes



I'w argraffu ar bapur â phennawd lleol

Ffurflen Gydsyniad Gwybodus i Gleifion ar gyfer Gofrestru ar:-

Hap-dreial dan reolaeth o chwistrelliad o adalimumab wrth ochr plasebo ar gyfer cleifion sy'n cael triniaeth ffisiotherapi ar gyfer seiatica.

Acronym: Treialu Chwistrelliad Dan y Croen o Adalimumab Wrth Ochr Grŵp Safonol (*Subcutaneous Injection of Adalimumab Trial Compared with Control*) (SCIATiC)

Enw yr ymchwilydd'.....

Rhif adnabod y cyfranogwr:…….

Rhowch lythrennau blaen eich enw ym mhob blwch

1. Cadarnhaf fy mod wedi darllen a deall y daflen wybodaeth i gyfranogwyr, rhan 1, sef Taflen Fersiwn 3, dyddiedig 16Mawrth 2016, ar gyfer yr astudiaeth uchod, ac imi gael cyfle i ofyn cwestiynau ynglŷn â'r astudiaeth. ☐

2. Rwy'n deall fy mod yn cydsynio i gofrestru ar gyfer astudiaeth SCIATIC, fy mod yn cymryd rhan yn wirfoddol ac y gallaf dynnu'n ôl unrhyw bryd, heb roi rheswm. Deallaf, os byddaf yn tynnu'n ôl, na fydd hynny'n effeithio o gwbl ar fy ngofal iechyd nac ar fy hawliau cyfreithiol. Os tynnaf yn ôl o'r astudiaeth, bydd yr ymchwilwyr yn defnyddio'r wybodaeth rwyf wedi'i rhoi hyd at yr adeg honno, oni nodaf nad wyf am iddynt wneud hynny. ☐

3. Rwy'n deall y caiff y wybodaeth a roddaf i'r ymchwilwyr ei defnyddio'n ☐

unig at ddibenion ymchwil, ac yr ymdrinnir yn gwbl gyfrinachol â manylion personol.

4. Rwyf wedi siarad â Dr /Mr /Ms _____ ☐

5. Deallaf fod gennyf hawl i dynnu'n ôl o'r astudiaeth:
   - ar unrhyw adeg.
   - heb orfod rhoi rheswm. ☐
   - heb i hynny effeithio fy ngofal meddygol.

6. Deallaf y bydd unigolion sy'n gysylltiedig â'r treial neu o awdurdodau rheoleiddiol lle mae hynny'n berthnasol i'm rhan yn yr ymchwil yn cyrchu a defnyddio rhannau o'm nodiadau meddygol. Rhoddaf ganiatâd i'r unigolion hyn gyrchu fy nghofnodion GIG, yn cynnwys nodiadau ysbyty, nodiadau gan fy meddyg teulu a nodiadau ffisiotherapi, ac i fanylion o'r cofnodion hyn gael eu cysylltu â data'r treial, er mwyn rhoi mwy o wybodaeth i ategu'r ymchwil. Caiff unrhyw wybodaeth a roddir ei thrin yn GWBL GYFRINACHOL. Defnyddir y wybodaeth hon ar gyfer ymchwil feddygol yn unig, ac ni fydd modd i neb fy adnabod ond wrth rif yn y treial, llythrennau blaen fy enw a'm dyddiad geni. Ni fydd modd fy adnabod o gwbl mewn dadansoddiad o'r canlyniadau na phan adroddir arnynt. ☐

7. Caniatâf i'm meddyg teulu gael gwybod fy mod yn cymryd rhan yn yr astudiaeth. ☐

8. Cytunaf i gael fy nghofrestru ar gyfer yr astudiaeth. ☐

Llofnod y Claf: _____

Enw mewn priflythrennau: _____

Dyddiad: _____

Llofnod y Ffisiotherapydd Ymchwil neu'r _____

Meddyg:

Enw'r Ffisiotherapydd Ymchwil neu'r Meddyg mewn priflythrennau: _____

Dyddiad: _____

Llofnod Cynrychiolydd y Claf _____

(os yw'n briodol):

Enw'r cynrychiolydd mewn priflythrennau: _____

Perthynas y Cynrychiolydd â'r claf: _____

Dyddiad: _____

Pan fydd y ffurflen wedi'i llenwi, rhowch gopi i'r cyfranogwr; copi ar gyfer ffeil gwefan yr ymchwilydd; a ffeiliwch y gwreiddiol yn nodiadau meddygol y claf.



l'w argraffu ar bapur â phennawd lleol

Ffurflen Gydsynio i Gleifion ar gyfer Hap-dreial:

Hap-dreial dan reolaeth o chwistrelliad o adalimumab wrth ochr plasebo ar gyfer cleifion sy'n cael triniaeth ffisiotherapi ar gyfer seiatica.

Acronym Treialu Chwistrelliad Dan y Croen o Adalimumab Wrth Ochr Grŵp Safonol (*Subcutaneous Injection of Adalimumab Trial Compared with Control*) (SCIATiC)

Enw yr ymchwilydd'.....

Rhif adnabod y cyfranogwr:…….

		Rhowch lythrennau blaen eich enw
1.	Cadarnhaf fy mod wedi darllen a deall y daflen wybodaeth i gyfranogwyr, Taflen Fersiwn 3, dyddiedig 16 Mawrth 2016, ar gyfer yr astudiaeth uchod, ac imi gael cyfle i ofyn cwestiynau ynglŷn â'r astudiaeth.	☐
2	Rwy'n deall fy mod yn cydsynio i gael prawf ar hap yn astudiaeth SCIATIC, fy mod yn cymryd rhan yn wirfoddol ac y gallaf dynnu'n ôl unrhyw bryd, heb roi rheswm. Deallaf, os byddaf yn tynnu'n ôl, na fydd hynny'n effeithio o gwbl ar fy ngofal iechyd nac ar fy hawliau cyfreithiol. Os tynnaf yn ôl o'r astudiaeth, bydd yr ymchwilwyr yn defnyddio'r wybodaeth rwyf wedi'i rhoi hyd at yr adeg honno, oni nodaf nad wyf am iddynt wneud hynny.	☐
3.	Rwy'n deall y caiff y wybodaeth a roddaf i'r ymchwilwyr ei defnyddio'n unig at ddibenion ymchwil, ac yr ymdrinnir yn gwbl gyfrinachol â manylion personol.	☐
4.	Rwyf wedi siarad â Dr /Mr /Ms _____	☐
5.	Deallaf fod gennyf hawl i dynnu'n ôl o'r astudiaeth: - ar unrhyw adeg.	☐

- heb orfod rhoi rheswm.
- heb i hynny effeithio fy ngofal meddygol.

6. Deallaf y bydd unigolion sy'n gysylltiedig â'r treial neu o awdurdodau rheoleiddiol lle mae hynny'n berthnasol i'm rhan yn yr ymchwil yn cyrchu a defnyddio rhannau o'm nodiadau meddygol. Rhoddaf ganiatâd i'r unigolion hyn gyrchu fy nghofnodion GIG, yn cynnwys nodiadau ysbyty, nodiadau gan fy meddyg teulu a nodiadau ffisiotherapi, ac i fanylion o'r cofnodion hyn gael eu cysylltu â data'r treial, er mwyn rhoi mwy o wybodaeth i ategu'r ymchwil. Caiff unrhyw wybodaeth a roddir ei thrin yn GWBL GYFRINACHOL. Defnyddir y wybodaeth hon ar gyfer ymchwil feddygol yn unig, ac ni fydd modd i neb fy adnabod ond wrth rif yn y treial, llythrennau blaen fy enw a'm dyddiad geni. Ni fydd modd fy adnabod o gwbl mewn dadansoddiad o'r canlyniadau na phan adroddir arnynt. ☐
7. Caniatâf i'm meddyg teulu gael gwybod fy mod yn cymryd rhan yn yr astudiaeth. ☐
8. Cytunaf i gymryd rhan yn yr astudiaeth. ☐
9. Cytunaf i gael prawf ar hap yn astudiaeth SCIATiC. ☐

Llofnod y Claf: _____

Enw mewn priflythrennau: _____

Dyddiad: _____

Llofnod y Meddyg: _____

Enw'r meddyg mewn priflythrennau: _____

Dyddiad: _____

Llofnod Cynrychiolydd y Claf _____

(os yw'n briodol):

Enw'r cynrychiolydd mewn priflythrennau: _____

Perthynas y Cynrychiolydd â'r claf: _____

Dyddiad: _____

Pan fydd y ffurflen wedi'i llenwi, rhowch gopi i'r cyfranogwr; copi ar gyfer ffeil gwefan yr ymchwilydd; a ffeiliwch y gwreiddiol yn nodiadau meddygol y claf.

Appendix 12 Case report forms including telephone screening and baseline questionnaire

Patient Hospital Number | | | | | | | |

SCIATIC

SubCutaneous Injection of Adalimumab Trial Compared with Control

Date of Call: ☐☐ ☐☐ ☐☐☐☐

DD **MM** **YYYY**

Time of Call: ☐☐ ☐☐

Hrs **mins**

Name of Caller: _____

Is the patient experiencing any of the following?

Please check these inclusion criteria for the participant and tick the appropriate box for each row:

		YES	NO
1	Are they aged 18 years or older?		
2	Current leg pain worse than, or as bad as, back pain		
3	Unilateral leg pain approximating a dermatomal distribution (contralateral buttock pain permitted if it does not extend below the inferior gluteal margin)		
4	Have they had persistent symptoms of the above for less than 22 weeks?		
5	Are they using a method of contraception? *(please note women who are pre-menopausal or not surgically sterile, must have a negative pregnancy test within two weeks of entering the trial)*		

Please check these exclusion criteria for the participant and tick the appropriate box for each row:

		YES	NO
6	Have their Sciatica symptoms persisted for longer than six months?		
7	Prior use of biological agents targeting TNF-alpha within the previous six months?		
8	Previous spinal surgery?		
9	Contra-indications to adalimumab injection including serious infection such as active or latent tuberculosis, transplanted organ, demyelinating disorders, malignancy, cardiac failure?		
10	Contra-indications to MRI including metal implants, potential metallic intra-ocular foreign bodies, claustrophobia?		
11	Pregnant, possibly pregnant or lactating?		
12	Unable to communicate in English or Welsh?		
13	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).*		

If the participant answers **YES** to question 1 to 5 then invite to clinic for eligibility check, consenting and screening, if participant answers **Yes** to Question 6 to 13 then participant is excluded.

Is the participant eligible? Yes ☐ No ☐

Participants Date of Birth ☐☐ ☐☐ ☐☐☐☐

DD **MM** **YYYY**

Date of 1st clinical appointment assessment screening:

☐☐ ☐☐ ☐☐☐☐

DD **MM** **YYYY**

Participant Identification Number

SCIATiC

SubCutaneous Injection of Adalimumab Trial Compared with Control

CASE REPORT FORM

CRF Completion Instructions for researchers

General

Complete the CRF using a **ballpoint pen** and ensure that all entries are complete and legible.

Avoid the use of abbreviations and acronyms.

The CRF should be completed as soon as possible after the scheduled visit.

Do not use subject identifiers anywhere on the CRF, such as name, hospital number etc., in order to maintain the confidentiality of the participant. Ensure that the header information (i.e. participant identification number) is completed consistently throughout the CRF.

Each CRF page should be signed and dated by the person completing the form.

The 'completed by' Name in the footer of each page must be legible and **CRFs should only be completed by individuals delegated to complete CRFs on the Site Delegation log (and signed by the PI).**

Ensure that all fields are completed on each page:

- If a test was Not Done record **ND** in the relevant box(es)
- Where information is Not Known write **NK** in relevant box(es)
- Where information is not applicable write **NA** in the relevant box(es)

Corrections to entries

If an error is made, draw a single line through the item, then write the correct entry on an appropriate blank space near the original data point on the CRF and initial and date the change.

Do NOT

- Obscure the original entry by scribbling it out
- Try to correct/ modify the original entry
- Use Tippex or correction fluid

Medications taken by the participant during the trial should be recorded on the "Concomitant Medications Log" using the generic name whenever possible, except combination products which will be recorded using the established trade name. All non-IMPs mentioned in the protocol should also be recorded on the "Concomitant medication Log" for the duration of the trial.

Verbatim Adverse Event terms (initial medical term) should be recorded as the final diagnosis whenever possible.

Complete all **dates** as day, month, year i.e. 13/11/2008. Partial dates should be recorded as NK/11/2008.

All **times** are to be recorded in 24 hour format without punctuation and always use 4-digits; i.e. 0200 or 2130. Midnight is recorded as 0000.

Weights should be recorded to the nearest 0.1 kg.

Source documents such as lab reports, ECG reports etc. should be filed separately from the CRF (if not in the medical notes) for each participant and be signed and dated by a delegated Investigator as proof of review of the assessment during the trial

If a subject prematurely withdraws from the trial a single line must be drawn across each uncompleted page to correspond with the last visit of the subject as mentioned on the "Trial Completion" page.

The Chief Investigator (for lead site)/Principal Investigator is responsible for the accuracy of the data reported on the CRF. The CI/PI must sign and date the Principal Investigator's Sign Off (below) to certify accuracy, completeness and legibility of the data reported in the CRF.

Serious Adverse Events (SAEs)

SAEs should be emailed **within 24 hours** of the site being aware of the event using the trial specific SAE report form **emailed toSCIATiCSAE@bangor.ac.uk**

Storage

CRF documents should be stored in a locked, secure area when not in use where confidentiality can be maintained. Ensure that they are stored separately to any other documents that might reveal the identity of the participant

Participant Identification Number ☐☐☐☐☐☐☐

FIRST CLINICAL ASSESSMENT DEMOGRAPHIC DATA

Date of Assessment:

☐☐ ☐☐ ☐☐☐☐

(DD/MM/YYYY)

Informed Consent:	
Date participant signed written consent form 1: ☐☐ ☐☐ ☐☐☐☐ (DD / MM / YYYY)	**Date of first trial-related procedure:** ☐☐ ☐☐ ☐☐☐☐ (DD / MM / YYYY)
Name of person taking informed consent: _____	
Please give a copy of the Participant Information Sheet and signed copy of the informed consent form to the participant; a copy for the researcher site file; and file the original in the participants' medical note.	

Please provide participant with SCIATiC– First Clinical Assessment Oswestry Disability Index Questionnaire

Has the participant moderate to high severity (≥30) on Oswestry Disability Index?

Yes ☐ No ☐

Completed by :.....Date:.....

Demographic Data:								
Date of Birth:		☐☐☐☐☐☐☐☐ (DD / MM / YYYY)						
Ethnicity:								
White	English	☐	Welsh	☐	Scottish	☐	Northern Irish	☐
	British	☐	Irish	☐	Gypsy or Irish traveller	☐	Other White background please describe below	☐
Comments:-								
Mixed / multiple ethnic groups	White & Black Caribbean	☐	White & Black African	☐	Other Mixed / Multiple ethnic background, please describe below	☐		
Comments:-								
Asian / Asian British	Indian	☐	Pakistani	☐	Bangladeshi	☐		
	Chinese	☐	Other Asian, please describe below			☐		
Comments:-								
Black / African / Caribbean / Black British	African	☐	Caribbean	☐	Other Black / African / Caribbean background, please describe below	☐		
Comments:-								
Other ethnic group	Arab	☐	Other ethnic group, please describe below			☐		
Comments:-								

Completed by :.....Date:.....

Sex: ☐ Male ☐ Female	
Height (cm): ☐☐☐	**Weight** (Kg): ☐☐.☐☐

Employment Status:

Employed – full time ☐ Employed – part time ☐

Self-employed ☐ Student ☐

House wife/husband ☐ Retired ☐

Unemployed ☐

Is the participant currently absent from work due to sciatica? Yes ☐ No ☐

Not applicable ☐

If **yes**, have they been:

Self-certified ☐ Certified sick by their doctor ☐

Other ☐ Please specify…….

Pain Assessment

Is the participant experiencing the following:-

Leg pain worse or as bad as back pain Yes ☐ No ☐

Unilateral leg pain approximating a dermatomal distribution Yes ☐ No ☐

Has the participant experienced their current episode for less than 22 weeks? Yes ☐ No ☐

How long have they being experiencing their current episode of sciatica?

☐☐☐ Weeks

Have they had a previous episode of sciatica in the last ☐ ☐

six months? Yes No

If they have had a previous episode have they been pain free

for at least one month before this current episode? Yes ☐ No ☐
N/A ☐

Completed by :.....Date:.....

How long is it since they had a whole month without any sciatica symptoms?

Less than three month ☐

Three to six months ☐

Seven to twelve months ☐

One to two years ☐

Three to five years ☐

Six to ten years ☐

More than ten years ☐

Eligible patients must have persistent sciatica for at least 4 weeks and less than 4 months

Completed by :.....Date:.....

FIRST CLINICAL ASSESSMENT MEDICAL HISTORY

Previous Medical History

Has the participant had any relevant medical history?	Please tick Yes* *Complete below*	Please tick No
Cauda equina syndrome		
Malignancy		
Recent spinal fracture		
Serious Infection		
Disc prolapse		
Tuberculosis		
Transplanted organ		
Demyelinating disorder		
Cardiac failure		
Pregnant or possibly pregnant		
Lactating		
Previous lumbar spine surgery		
Widespread pain		
Use of biological agents within previous six months		

*If **YES** for any of the above, please give further details (including dates) and state if the condition is still active. If giving details of surgery please state the underlying cause. Use a separate line for each condition.

Details (Including Dates)	Currently Active Yes	No

Completed by :.....Date:.....

FIRST CLINICAL ASSESSMENT PHYSICAL EXAMINATION

Code	Examination Finding	Please tick *Abnormal	Please tick Normal
1	Straight leg raise left		
2	Straight leg raise right		
3	Femoral stretch test left		
4	Femoral stretch test right		
5	Muscle power		
6	Pin prick sensation		
7	Tendon reflexes		

*If Abnormal enter the code below boxes and give brief details. Please use a separate line for each condition

Code	Details

Completed by :.....Date:.....

DOI: 10.3310/hta21600

FIRST CLINICAL ASSESSMENT CONCOMITANT MEDICATIONS

Is the participant taken any concomitant medications at screening						☐ **No** ☐ **Yes,** Complete below		
Medication (Record Generic or trade name)	**Reason for use** (Medical History diagnosis or other reason, e.g. Prophylaxis)	Dose	units	**Frequency**	**Route**	**Start Date** (DD/MM/YYYY)	**Stop Date** (DD//MM/YYY)	**Or tick if ongoing at Screening Visit**
1.						☐☐ ☐☐ ☐☐☐☐	☐☐ ☐☐ ☐☐☐☐	☐
2.						☐☐ ☐☐ ☐☐☐☐	☐☐ ☐☐ ☐☐☐☐	☐
3.						☐☐ ☐☐ ☐☐☐☐	☐☐ ☐☐ ☐☐☐☐	☐
4.						☐☐ ☐☐ ☐☐☐☐	☐☐ ☐☐ ☐☐☐☐	☐
5.						☐☐ ☐☐ ☐☐☐☐	☐☐ ☐☐ ☐☐☐☐	☐
6.						☐☐ ☐☐ ☐☐☐☐	☐☐ ☐☐ ☐☐☐☐	☐
7.						☐☐ ☐☐ ☐☐☐☐	☐☐ ☐☐ ☐☐☐☐	☐
Please add additional concomitant medication logs as required						☐ **Please check box if this is the last page used**		

Completed by :.....Date:.....

FIRST CLINICAL ASSESSMENT INCLUSION/EXCLUSION CHECK

Part A: To be completed for all participants

Participants should only be entered into the SCIATiC study if the '**Yes**' box for each row under Inclusion Criteria has been ticked.

Inclusion criteria

Please check these inclusion criteria for the participant and tick the appropriate box for each row:

	YES	NO
Are they aged 18 years or older?		
Current leg pain worse than, or as bad as, back pain		
Unilateral leg pain approximating a dermatomal distribution (contralateral buttock pain permitted if it does not extend below the inferior gluteal margin)		
At least one of the following:- • Positive straight leg raise test (SLR) restricted <50 degrees by leg pain • Positive femoral stretch test • Muscle weakness in one myotome • Loss of tendon reflex • Loss of sensation in a dermatomal distribution		
Have they had persistent symptoms of the above for less than 22 weeks?		
Have they scored moderate to high severity (≥30) on the Oswestry Disability Index?		
Are they using a method of contraception? *(please note women who are pre-menopausal or not surgically sterile), must have a negative pregnancy test within two weeks of entering the trial)*		
Have they given informed consent?		

Completed by :.....Date:.....

Participants should only be entered into the SCIATiC study if the '**No**' box for each row under Exclusion Criteria has been ticked.

Exclusion criteria

Please check these exclusion criteria for the participant and tick the appropriate box for each row:

	YES	NO
Have their Sciatica symptoms persisted for longer than six months?		
Suspected serious spinal pathology, including cauda equina syndrome, malignancy, fracture or infection?		
Prior use of biological agents targeting TNF-alpha within the previous six months?		
Previous spinal surgery?		
Contra-indications to adalimumab injection including serious infection such as active or latent tuberculosis, transplanted organ, demyelinating disorders, malignancy, cardiac failure?		
Contra-indications to MRI including metal implants, potential metallic intra-ocular foreign bodies, claustrophobia?		
Pregnant, possibly pregnant or lactating?*		
Unable to communicate in English or Welsh?		

- Please ensure that response to pregnancy or possibly pregnant is the same as at the first assessment on page 9, if not please clarify with the participant

Is the participant eligible to take part in the study? Yes ☐ No ☐

If eligible to participate in the study please register the participant.

Completed by :.....Date:.....

If participant has consented to take part in the study please confirm the participant has been sent for the following:

Blood tests:	**Yes**	**No**	**Not applicable**
FBC	☐	☐	
U&E	☐	☐	
LFT	☐	☐	
Hba1c	☐	☐	
eGFR	☐	☐	
TB screening which may include CXR	☐	☐	
Biological agent counselling	☐	☐	
Pregnancy test	☐	☐	☐
MRI scan	☐	☐	

Completed by :.....Date:.....

SECOND CLINICAL ASSESSMENT

Date of Assessment:

☐☐ ☐☐ ☐☐☐☐

DD MM YYYY

Pain Assessment

Is the patient still experiencing the following?

Leg pain worse or as bad as back pain Yes ☐ No ☐

Unilateral leg pain approximating a dermatomal distribution Yes ☐ No ☐

Has the participant experienced their current episode of sciatica for more than four weeks? Yes ☐ No ☐

Has the participant experienced their current episode of sciatica for less than 26 weeks? Yes ☐ No ☐

Please provide participant with SCIATiC– Second Clinical Assessment Oswestry Disability Index Questionnaire

Has the participant moderate to high severity (≥30) on Oswestry Disability Index?

Yes ☐ No ☐

Completed by :.....Date:.....

Lab Analysis:

Sample Required	**Date Sample Taken (DD/MM/YYYY**
Full Blood Count	☐☐ ☐☐ ☐☐☐☐
Liver Function Test	☐☐ ☐☐ ☐☐☐☐
Urea and Electrolytes	☐☐ ☐☐ ☐☐☐☐
HbA1C	☐☐ ☐☐ ☐☐☐☐
eGFR	☐☐ ☐☐ ☐☐☐☐

Are all final results Normal ☐ Abnormal ☐

Please note if results are abnormal and clinically significant further discussion will be required with the rheumatologist.

Abnormal results after discussion with rheumatologist

Abnormal (Not Clinically Significant) ☐ **Abnormal (Clinically Significant) ☐

**Description:----------

Pregnancy test (if applicable):

Date: ☐☐ ☐☐ ☐☐☐☐

Positive ☐ Negative ☐

Not applicable ☐

Completed by :.....Date:.....

TB screening

Date: ☐☐ ☐☐ ☐☐☐☐

Positive ☐ Negative ☐

Biological counselling given:

Yes ☐ No ☐

Biological counselling given by: _____

Date of counselling: ☐☐ ☐☐ ☐☐☐☐

MRI scan

Date: ☐☐ ☐☐ ☐☐☐☐

Result- Serious Spinal Pathology Absent?

Yes ☐ No ☐

Does any results contradict study entry?

Yes* ☐ No ☐

If *Yes participant must not continue.

Completed by :.....Date:.....

Reconfirmation of Inclusion & Exclusion Criteria

Part A: To be completed for all patients

Participants should only be entered into the SCIATiC study if the '**Yes**' box for each row under Inclusion Criteria has been ticked.

Inclusion criteria

Please check these inclusion criteria for the participant and tick the appropriate box for each row:

	YES	NO
Are they aged 18 years or older?		
Current leg pain worse than, or as bad as, back pain?		
Unilateral leg pain approximating a dermatomal distribution (contralateral buttock pain permitted if it does not extend below the inferior gluteal margin)?		
One of the following:- • Positive straight leg raise test (SLR) restricted <50 degrees by leg pain • Positive femoral stretch test • Muscle weakness in one myotome • Loss of tendon reflex • Loss of sensation in a dermatomal distribution		
Have they had persistent symptoms of the above for at least four weeks and less than 26 weeks?		
Have they scored moderate to high severity (≥30) on the Oswestry Disability Index?		
Are they using a method of contraception? *(please note women who are pre-menopausal or not surgically sterile), must have a negative pregnancy test within two weeks of entering the trial)*		

Completed by :.....Date:.....

Participants should only be entered into the SCIATiC study if the '**No**' box for each row under Exclusion Criteria has been ticked.

Exclusion criteria

Please check these exclusion criteria for the participant and tick the appropriate box for each row:

	YES	NO
Have their symptoms persisted for longer than six months?		
Presence of serious spinal pathology, including cauda equina syndrome, malignancy, fracture or infection?		
Prior use of biological agents targeting TNF-alpha within the previous six months?		
Previous spinal surgery?		
Contra-indications to adalimumab injection including serious infection such as active or latent tuberculosis, transplanted organ, demyelinating disorders, malignancy, cardiac failure?		
Contra-indications to MRI including metal implants, potential metallic intra-ocular foreign bodies, claustrophobia?		
Pregnant, possibly pregnant or lactating?		
Unable to communicate in English or Welsh?		

Is the participant eligible to take part in the study?

Yes ☐ No ☐

If participant is eligible to participate in the study please give Patient Information Sheet and Informed Consent Form part two to patient

Completed by :.....Date:.....

Informed Consent:

Has the participant given informed consent?

Yes ☐ *** No** ☐

Date participant signed written consent form 2: ☐☐ ☐☐ ☐☐☐☐

DD / MM/ YYY

Name of person taking informed consent: _____

Please give a copy of the signed copy of the informed consent form to the participant; a copy for the researcher site file; and file the original in the participants' medical note.

If no, Participant unable to proceed further

Completed by :.....Date:.....

Part B: To be completed if participant is eligible to take part in the study

SECOND CLINICAL ASSESSMENT PARTICIPANT ELIGIBILITY REVIEW			
Document	**Completed**	**Reason for non-completion**	**Initials of researcher**
Eligibility criteria			
Consent form 1			
1st Clinical assessment screening booklet			
Consent form 2			
2nd Clinical assessment screening booklet			
Baseline questionnaire booklet			

If participant has consented please confirm the following:

Participant's eligibility Investigator Sign-Off:	
Is the participant eligible to take part in the Clinical Trial? ☐☐ ☐☐ ☐☐☐☐ (DD / MM / YYYY)	☐Yes ☐No, Please give reason for screen failure below
Reason(s) for screen failure:	
1.	
2.	
3.	

If the participant decided not to consent, did they indicate the reason for this? (*It is not compulsory for the participant to answer this question)*

Burden on time ☐
Did not want to be randomised ☐
Did not want to be in a research study ☐
Did not want to answer questionnaires ☐
Other (*please specify)* ☐

Completed by :.....Date:.....

Participant Randomisation	
Date of Randomisation	☐☐ ☐☐ ☐☐☐☐ (DD / MM / YYYY)

Completed by :.....Date:.....

Date of Assessment:

☐☐ ☐☐ ☐☐☐☐

(DD/MM/YYYY)

FIRST TRIAL MEDICATION ADMINISTRATION

If treatment is not given on date of randomisation please ask participant the following:

		Yes	No
1.	**Have there been any new Adverse Events?** (If yes, please record in Adverse Events page)	☐	☐
2.	**Have there been any changes in Concomitant Medications?** (If yes, please record in Concomitant Medications Log)	☐	☐

Details of who was present at time of first injection

Name **Job Title** **Signature** **Date(DD/MM/YYYY**

SCIATiC Trial Administration

Date of Dosing (DD/MM/YYYY)	**Dose**	**Units**	**Was the participants treatment dose :-**		
			Interrupted	**Yes** ☐	**No** ☐
			Dose checking	Batch Number	

Completed by :.....Date:.....

Was the 1st Injections given on same day as randomisation?

YES ☐ NO ☐

If no, please provide details:-

……

……

……

Which treatment does the participant consider they have received today?

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 ☐

Arrange participant to attend physiotherapy intervention

Completed by :……Date:……

PHYSIOTHERAPY INTERVENTION COVER SHEET

Number of physiotherapy courses given to participant: ☐

Treatment start date: ☐☐ ☐☐ ☐☐☐☐

DD/MM/YYYY

Treatment Stop date: ☐☐ ☐☐ ☐☐☐☐

DD/MM/YYYY

Outcome of treatment:

Discharged back to GP care ☐

Referred to interface services ☐

Referred to spinal orthopaedics or neurosurgery ☐

Physiotherapy intervention form completed? Yes ☐ No ☐

If no, please provide details:-

……

……

Completed by :……Date:……

Date of Assessment:

☐☐ ☐☐ ☐☐☐☐

(DD/MM/YYYY)

SECOND TRIAL MEDICATION ADMINSTRATION

Date of Visit: ☐☐ ☐☐ ☐☐☐☐

(DD / MM / YYYY)

Visit Checklist:

		Yes	No
1.	**Have there been any new Adverse Events?** (If yes, please record in Adverse Events page)	☐	☐
2.	**Have there been any changes in Concomitant Medications?** (If yes, please record in Concomitant Medications Log)	☐	☐

Is the participant still able to receive the second injection?

Yes ☐ No ☐

If no please provide further details:

……

……

Is the participant eligible to continue?

Yes ☐ No ☐

Completed by :……Date:……

Prior to the patient receiving their second injection please ask which treatment does the participant consider they have received today?

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 ☐

Details of who was present at time of second injection

Name **Job title** **Signature** **Date**

SCIATiC Trial Administration

Date of Dosing (DD/MM/YYYY)	**Dose**	**Units**	**Was the participants treatment dose :-**		
☐☐ ☐☐ ☐☐☐☐			**Delayed**	**Yes** ☐	**No** ☐
			Interrupted	**Yes** ☐	**No** ☐
			Dose checking	Batch Number	

Completed by :.....Date:.....

Post second injection please ask which treatment does the participant consider they have received today?

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	☐

Completed by :.....Date:.....

ADVERSE EVENTS PAGE

Part A (to be completed by Researcher, Research nurse or Principal Investigator at the treatment site.)

SCIATiC Trial Adverse Event Report	
Date of report	_ _/_ _/ _ _ _ _
Details of adverse event	
Comments (if applicable) **Have there been any changes in Concomitant Medications?** (If yes, please record in Concomitant Medications Log) Onset (dd/mm/yyyy)	_ _/_ _/ _ _ _ _
Severity	Mild ☐ Moderate ☐ Severe ☐
Relationship to SCIATiC treatment	Not related ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely ☐
Expectedness	Expected ☐ Unexpected ☐
AE outcome	Resolved ☐ Resolved with sequaelae ☐ Persisting ☐ Death ☐ Unknown ☐
Resolution date (dd/mm/yyyy)	_ _/_ _/ _ _ _ _
Reported as serious?	YES ☐ NO ☐

If adverse event is deemed as serious PI to complete part B

Completed by :.....Date:.....

Part B (to be completed by Principal Investigator)

Action Taken as Result of Serious Adverse Event:	
☐ None	*Give detail, including new dose (units), date(s) of administration and duration:*
☐ Dose changed	
☐ Medication interrupted	
☐ Medication discontinued	
☐ Other *(i.e. Treated with concomitant medication(s))*	*Tick if **concomitant medication** is listed on a separate sheet and indicate number of pages*
☐ Unknown at time of report	☐ **Pages:**

Blinding Information			
Blind Broken:	☐ *No*	☐ *Yes*	☐ *Not Applicable*
Is the information on this form likely to un-blind the reviewer			
☐ *No*		☐ *Yes*	
if Yes send to unblinded reviewer			
☐ Continuing in the trial			
☐ Completed the trial	**Date of Completion:**	_ _/_ _/ _ _ _ _	
☐ Withdrawn from the trial	**Date of Withdrawal:**	_ _/_ _/ _ _ _ _	

Name of PI

Signature of PI

Date of signature _ _/_ _/ _ _ _ _

PI Confirmation - This form is completed satisfactorily ☐ *Yes* ☐ *No*

Part C (to be completed by Chief Investigator/ delegated reviewer)

Was SAE drug related ☐ *Yes* ☐ *No*

SAE event No ☐☐☐☐☐☐☐/☐☐

Was the event unexpected ☐ *Yes* ☐ *No*

Was the event a SUSAR ☐ *Yes* ☐ *No*

Comments

Name of reviewer

Signature of reviewer

Date of signature

__/__/____

Date sent to MHRA

(SUSAR only) __/__/____

CONCOMITANT MEDICATIONS LOG

Has the participant used any Concomitant Medications?						☐ **No** ☐ **Yes,** Complete below		
Medication (Record Generic or trade name)	**Reason for use** (Medical History diagnosis or other reason, e.g. Prophylaxis)	Dose	units	**Frequency**	**Route**	**Start Date** (DD/MM/YYYY)	**Stop Date** (DD//MM/YYY)	**Or tick if ongoing**
1.						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐
2.						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐
3.						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐
4.						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐
5.						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐
6.						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐
Please add additional concomitant medication logs as required						☐ **Please check box if this is the last page used**		

Note: Use the Concomitant log to record Non-IMPs

Completed by :.....Date:.....

WITHDRAWAL FORM

Please return to: SCIATiC trial manager NWORTH, Bangor University, Normal Site, Meirion Building, Holyhead Road, Bangor LL57 2DG

Centre Name: .....

If the SCIATiC participant can/will no longer fully comply with the SCIATiC protocol, please indicate the level that they wish to withdraw below:

1.	Patient does not wish to participate in further SCIATiC trial treatment but gives consent for data regarding their health status to be collected	☐	0=No 1=Yes
2	Patient does not wish to participate in any aspect of the SCIATiC trial and withdraws consent for any data to be collected regarding their health status	☐	0=No 1=Yes
3	Patient would like to give their reason(s) for withdrawing (this is completely optional).	☐	0=No 1=Yes

If question 3 has been answered "Yes", please write the participant's reasons below, or attach a separate sheet.

I confirm that the information provided above is correct to the best of my knowledge, and that I have taken a copy for the participants file.

Signed by (authorised person) .....
Print name.....

Date of completion ..... / ..... / .....

TRIAL COMPLETION

Date finished study: ☐☐ ☐☐ ☐☐☐☐

DD/MM/YYY

Date last study medication given: ☐☐ ☐☐ ☐☐☐☐

DD/MM/YYYY

REASON FINISHED STUDY

Please only mark the primary reason. All reasons other than 'COMPLETED STUDY' require an explanation next to the response.

☐ Completed study

☐ AE/SAE (complete AE CRF and SAE form if applicable)

☐ Lost to follow-up

☐ Non-compliant participant

☐ Concomitant medication

☐ Medical Contraindication

☐ Consent withdrawn –*if withdrawn please complete withdrawal form*

☐ Death (complete SAE form)

☐ Other *(specify*……..

……

……

Principal Investigator's Sign Off

I have reviewed this CRF and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant. All entries were made either by me or by a person under my supervision who has signed the Delegation and Signature Log.

Centre Name: _____

Principal Investigator's Name:
(Please print name): _____

Principal Investigator's Signature: _____

Date: ☐☐ ☐☐ ☐☐☐☐
(DD/MM/YYYY)

ONCE SIGNED NO FURTHER CHANGES CAN BE MADE TO THIS CRF WITHOUT AUTHORISATION.

SubCutaneous

Injection of

Adalimumab

Trial Compared with

Control

S.7 PHYSIOTHERAPY INTERVENTION FORM

Please keep this form attached to physiotherapy notes. On discharge this must be sent to (*please provide details of local SCIATiC trial co-ordinator) for upload to MACRO system.*

Participant ID number ☐☐☐☐☐☐☐	Name of Physiotherapist: Treatment Site:

General summary of patient's problem and diagnosis/clinical impression:

Location of pain

Neural Tension Test:

Neurological deficit:

Oswestry Disability Score:

Comments:

Dates Participants Did Not Attend: ……./……./……., ……./……./……., ……./……./……., Total Number: ☐ Dates Participants Could not attend: ……./……./……., ……./……./……., ……./……./……., Total Number: ☐	Total Visits: ☐ Duration of treatment (weeks) ☐

Date attended	Did the participant experience an AE or SAE? Yes ☐ No ☐ If yes please provide details of event to research physiotherapist, with start and stop dates and treatment given: *(ensure an AE/SAE form in the CRF is completed)* Any changes to Conmeds? Yes ☐ No ☐ If yes please provide details to research physiotherapist to update conmed sheet	.. / .. / ..	Did the participant experience an AE or SAE? Yes ☐ No ☐ If yes please provide details of event to research physiotherapist, with start and stop dates and treatment given: *(ensure an AE/SAE form in the CRF is completed)* Any changes to Conmeds? Yes ☐ No ☐ If yes please provide details to research physiotherapist to update conmed sheet	.. / .. / ..	Did the participant experience an AE or SAE? Yes ☐ No ☐ If yes please provide details of event to research physiotherapist, with start and stop dates and treatment given: *(ensure an AE/SAE form in the CRF is completed)* Any changes to Conmeds? Yes ☐ No ☐ If yes please provide details to research physiotherapist to update conmed sheet	.. / .. / ..

Modalities Used (please tick ✓)	Date	✓	Date	✓	Date	✓
Advice & education & reassurance						
Medication usage discuss/review						
Specific exercise: Stability						
Specific exercise: McKenzie						
Specific exercise: Neural glides						
Specific exercise: Other						
Joint mobilisations/ manipulations						
Soft tissue techniques						
Other treatment (give details)						
Action plan for relapse discussed						

Outcome e.g. onwards referral or discharge	
	Discharged back to GP care ☐
	Referred to interface services ☐
	Referred to spinal orthopaedics or neurosurgery ☐

Any comments:

Date attended						
	Did the participant experience an AE or SAE? Yes ☐ No ☐ If yes please provide details of event to research physiotherapist, with start and stop dates and treatment given: *(ensure an AE/SAE form in the CRF is completed)* Any changes to Conmeds? Yes ☐ No ☐ If yes please provide details to research physiotherapist to update conmed sheet	.. / .. / ..	Did the participant experience an AE or SAE? Yes ☐ No ☐ If yes please provide details of event to research physiotherapist, with start and stop dates and treatment given: *(ensure an AE/SAE form in the CRF is completed)* Any changes to Conmeds? Yes ☐ No ☐ If yes please provide details to research physiotherapist to update conmed sheet	.. / .. / ..	Did the participant experience an AE or SAE? Yes ☐ No ☐ If yes please provide details of event to research physiotherapist, with start and stop dates and treatment given: *(ensure an AE/SAE form in the CRF is completed)* Any changes to Conmeds? Yes ☐ No ☐ If yes please provide details to research physiotherapist to update conmed sheet	.. / .. / ..

Modalities Used (please tick ✓)	Date	✓	Date	✓	Date	✓
Advice & education & reassurance						
Medication usage discuss/review						
Specific exercise: Stability						
Specific exercise: McKenzie						
Specific exercise: Neural glides						
Specific exercise: Other						
Joint mobilisations/ manipulations						
Soft tissue techniques						
Other treatment (give details)						

Action plan for relapse discussed	
Outcome e.g. onwards referral or discharge	Discharged back to GP care ☐ Referred to interface services ☐ Referred to spinal orthopaedics or neurosurgery ☐
Any comments:	

Has the participant used any Concomitant Medications?						☐ **No** ☐ **Yes,** Complete below		
Medication (Record Generic or trade name)	**Reason for use** (Medical History diagnosis or other reason, e.g. Prophylaxis)	Dose	units	**Frequency**	**Route**	**Start Date** (DD/MM/YYYY)	**Stop Date** (DD//MM/YYY)	**Or tick if ongoing**
1.						☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐	☐
2.						☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐	☐
3.						☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐	☐
4.						☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐	☐
5.						☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐	☐
6.						☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐	☐
Please add additional concomitant medication logs as required						☐ **Please check box if this is the last page used**		

CONCOMITANT MEDICATIONS LOG

Note: Use the Concomitant log to record Non-IMPs

Completed by :.....Date:.....

ADVERSE EVENTS PAGE

Part A **(to be completed by Researcher, Research nurse or Principal Investigator at the treatment site.)**

SCIATiC Trial Adverse Event Report	
Date of report	_ _/_ _/ _ _ _ _
Details of adverse event	
Comments (if applicable) **Have there been any changes in Concomitant Medications?** (If yes, please record in Concomitant Medications Log) Onset (dd/mm/yyyy)	_ _/_ _/ _ _ _ _
Severity	Mild ☐ Moderate ☐ Severe ☐
Relationship to SCIATiC treatment	Not related ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely ☐
Expectedness	Expected ☐ Unexpected ☐
AE outcome	Resolved ☐ Resolved with sequaelae ☐ Persisting ☐ Death ☐ Unknown ☐
Resolution date (dd/mm/yyyy)	_ _/_ _/ _ _ _ _
Reported as serious?	YES ☐ NO ☐

If adverse event is deemed as serious PI to complete part B

Please add additional adverse event pages as required ☐

Please check box if this is the last page used

Participant Identification Number ☐☐☐☐☐☐☐☐

SCIATiC

SubCutaneous Injection of Adalimumab Trial Compared with Control

This is an index used by clinicians and researchers to measure disability for low back pain. Please answer every section, and mark in each section only the ***one box*** which applies to you. We realise you may consider that two of the statements in any one section relate to you, but please ***just mark the box which most closely*** describes your problem.

Section 1 – Pain Intensity

- I can tolerate the pain I have without having to use pain killers. ❑
- The pain is bad but I manage without pain killers. ❑
- Pain killers give complete relief from pain. ❑
- Pain killers give moderate relief from pain. ❑
- Pain killers give very little relief from pain. ❑
- Pain killers have no effect on the pain and I do not use them. ❑

Section 2 – Personal Care (Washing, Dressing, etc)

- I can look after myself normally without causing extra pain. ❑
- I can look after myself normally but it causes extra pain. ❑
- It is painful to look after myself and I am slow and careful. ❑
- I need some help but manage most of my personal care. ❑
- I need help every day in most aspects of self care. ❑
- I do no get dressed, wash with difficulty and stay in bed. ❑

Section 3 - Lifting

- I can lift heavy weights without extra pain. ❑
- I can lift heavy weights but it gives extra pain. ❑
- Pain prevents me from lifting heavy weights off the floor but I can manage if they are conveniently positioned, eg on a table. ❑
- Pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned. ❑
- I can lift only very light weights. ❑
- I cannot lift or carry anything at all. ❑

Section 4 – Walking

Pain does not prevent me walking any distance. ❑

Pain prevents me walking more than 1 mile. ❑

Pain prevents me walking more than ½ mile. ❑

Pain prevents me walking more than ¼ mile. ❑

I can only walk using a stick or crutches. ❑

I am in bed most of the time and have to crawl to the toilet. ❑

Section 5 - Sitting

I can sit in any chair as long as I like. ❑

I can only sit in my favourite chair as long as I like. ❑

Pain prevents me sitting more than an hour. ❑

Pain prevents me from sitting more than ½ hour. ❑

Pain prevents me from sitting more than 10 mins. ❑

Pain prevents me from sitting at all. ❑

Section 6 – Standing

I can stand as long as I want without extra pain. ❑

I can stand as long as I want but it gives me extra pain. ❑

Pain prevents me from standing for more than 1 hour. ❑

Pain prevents me from standing for more than 30 mins. ❑

Pain prevents me from standing for more than 10 mins. ❑

Pain prevents me from standing at all. ❑

Section 7 – Sleeping

Pain does not prevent me from sleeping well. ❑

I can sleep well only by using tablets. ❑

Even when I take tablets I have less than six hours sleep. ❑

Even when I take tablets I have less than four hours sleep. ❑

Even when I take tablets I have less than two hours sleep. ❑

Pain prevents me from sleeping at all. ❑

Section 8 – Sex Life

My sex life is normal and causes no extra pain. ❑

My sex life I normal but causes some extra pain. ❑

My sex life is nearly normal but is very painful. ❑

My sex life is severely restricted by pain. ❑

My sex life is nearly absent because of pain. ❑

Pain prevents any sex life at all. ❑

Section 9 – Social Life

My social life is normal and gives me no extra pain. ❑

My social life is normal but increases the degree of pain. ❑

Pain has no significant effect on my social life apart from limiting my more energetic interests, eg dancing, etc. ❑

Pain has restricted my social life and I do not go out as often. ❑

Pain has restricted my social life to my home. ❑

I have no social life because of pain. ❑

Section 10 – Travelling

I can travel anywhere without extra pain. ❑

I can travel anywhere but it gives me extra pain. ❑

Pain is bad but I manage journeys over two hours. ❑

Pain restricts me to journeys of less than one hour. ❑

Pain restricts me to short necessary journeys under 30 min. ❑

Pain prevents me from travelling except to the doctors or hospital. ❑

Thank you for your time and co-operation in answering these questions.

Patient Identification Number: | | | | | | | |

SCIATiC

SubCutaneous Injection of Adalimumab Trial Compared with Control

Baseline Questionnaire

Participant Baseline Questionnaire Booklet

Thank you for participating in this research study. An important part of this study is the questionnaire booklet which has been designed to measure the effects of your illness and treatment.

The information you provide will be kept strictly confidential and used only for medical research.

Please note that your doctor, physiotherapist or nurse will not see the answers you give and, if you have specific symptoms or problems as indicated here, you may need to discuss these with your doctor, physiotherapist or nurse in person.

If you find any of the questions are irrelevant or difficult please make a note of this on the last page.

Please answer all the questions yourself by entering your responses that best applies to you, as instructed.

There are no “right” or “wrong” answers.

Please enter the date on which you completed this questionnaire: ...../...../.....

Pain trajectory

How long is it since they had a whole month without any sciatica symptoms?

- Less than three month ☐
- Three to six months ☐
- Seven to twelve months ☐
- One to two years ☐
- Three to five years ☐
- Six to ten years ☐
- More than ten years ☐

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

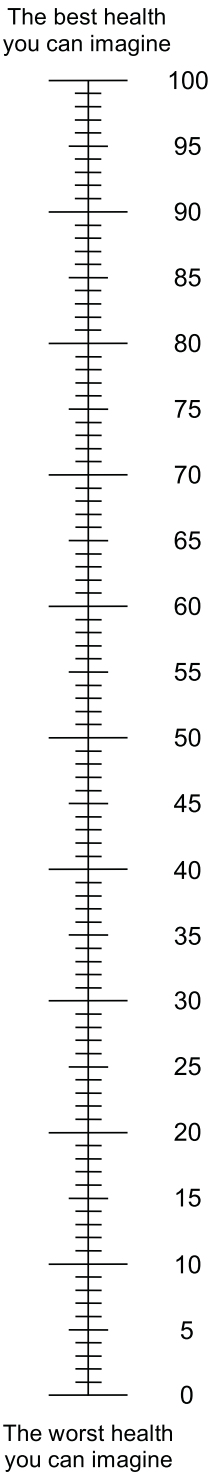
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Holiadur Iechyd

Fersiwn Cymraeg ar gyfer y Deyrnas Unedig

(Welsh version for Wales)

O dan bob pennawd, ticiwch yr UN blwch sy'n disgrifio eich iechyd chi HEDDIW orau.

SYMUDEDD

Dydw i ddim yn cael anhawster wrth gerdded o gwmpas ❑
Rydw i'n cael ychydig o anhawster wrth gerdded o gwmpas ❑
Rydw i'n cael anhawster cymedrol wrth gerdded o gwmpas ❑
Rydw i'n cael anhawster difrifol wrth gerdded o gwmpas ❑
Dydw i ddim yn gallu cerdded o gwmpas ❑

HUNAN-OFAL

Dydw i ddim yn cael anhawster ymolchi neu wisgo amdanaf ❑
Rydw i'n cael ychydig o anhawster ymolchi neu wisgo amdanaf ❑
Rydw i'n cael anhawster cymedrol ymolchi neu wisgo amdanaf ❑
Rydw i'n cael anhawster difrifol ymolchi neu wisgo amdanaf ❑
Dydw i ddim yn gallu ymolchi neu wisgo amdanaf ❑

GWEITHGAREDDAU ARFEROL *(e.e. gwaith, astudio, gwaith tŷ, gweithgareddau teuluol neu hamdden)*

Dydw i ddim yn cael anhawster gwneud fy ngweithgareddau arferol ❑
Rydw i'n cael ychydig o anhawster gwneud fy ngweithgareddau arferol ❑
Rydw i'n cael anhawster cymedrol gwneud fy ngweithgareddau arferol ❑
Rydw i'n cael anhawster difrifol gwneud fy ngweithgareddau arferol ❑
Dydw i ddim yn gallu gwneud fy ngweithgareddau arferol ❑

POEN / ANGHYSUR *(e.e. teimlo'n anghyfforddus)*

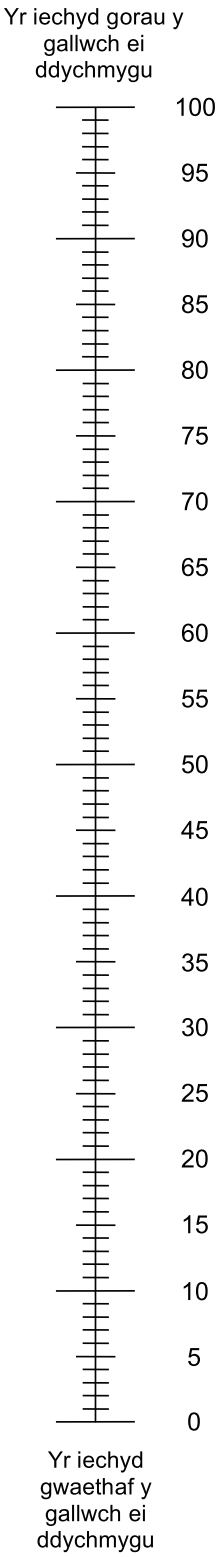
Does gen i ddim poen nac anghysur ❑
Mae gen i ychydig o boen neu anghysur ❑
Mae gen i boen neu anghysur cymedrol ❑
Mae gen i boen neu anghysur difrifol ❑
Mae gen i boen neu anghysur eithafol ❑

PRYDER / ISELDER

Dydw i ddim yn teimlo'n bryderus nac yn isel ❑
Rydw i'n teimlo ychydig yn bryderus neu isel ❑
Rydw i'n teimlo'n gymedrol o bryderus neu isel ❑
Rydw i'n teimlo'n ddifrifol o bryderus neu isel ❑
Rydw i'n teimlo'n eithafol o bryderus neu isel ❑

- Hoffem gael gwybod pa mor dda neu wael yw eich iechyd chi HEDDIW.
- Mae'r raddfa hon wedi ei rhifo o 0 i 100.
- Mae 100 yn golygu'r iechyd gorau y gallwch ei ddychmygu.
  Mae 0 yn golygu'r iechyd gwaethaf y gallwch ei ddychmygu.
- Rhowch X ar y raddfa i ddangos sut mae eich iechyd chi HEDDIW.
- Yn awr ysgrifennwch y rhif wnaethoch chi ei nodi ar y raddfa yn y blwch isod.

EICH IECHYD CHI HEDDIW = ☐



The following questionnaires were also used:

- leg pain version of RMDQ[38,41]
- STarT Back Tool[47]
- SBI[42]
- HADS[44]
- Graddfa Pryder ac Iselder Ysbyty (HADS)[44]
- RUQ[45,46]
- Pain Manikin[43]
- PSEQ[49]
- fear of movement using the TSK.[50]

EME
HS&DR
HTA
PGfAR
PHR

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