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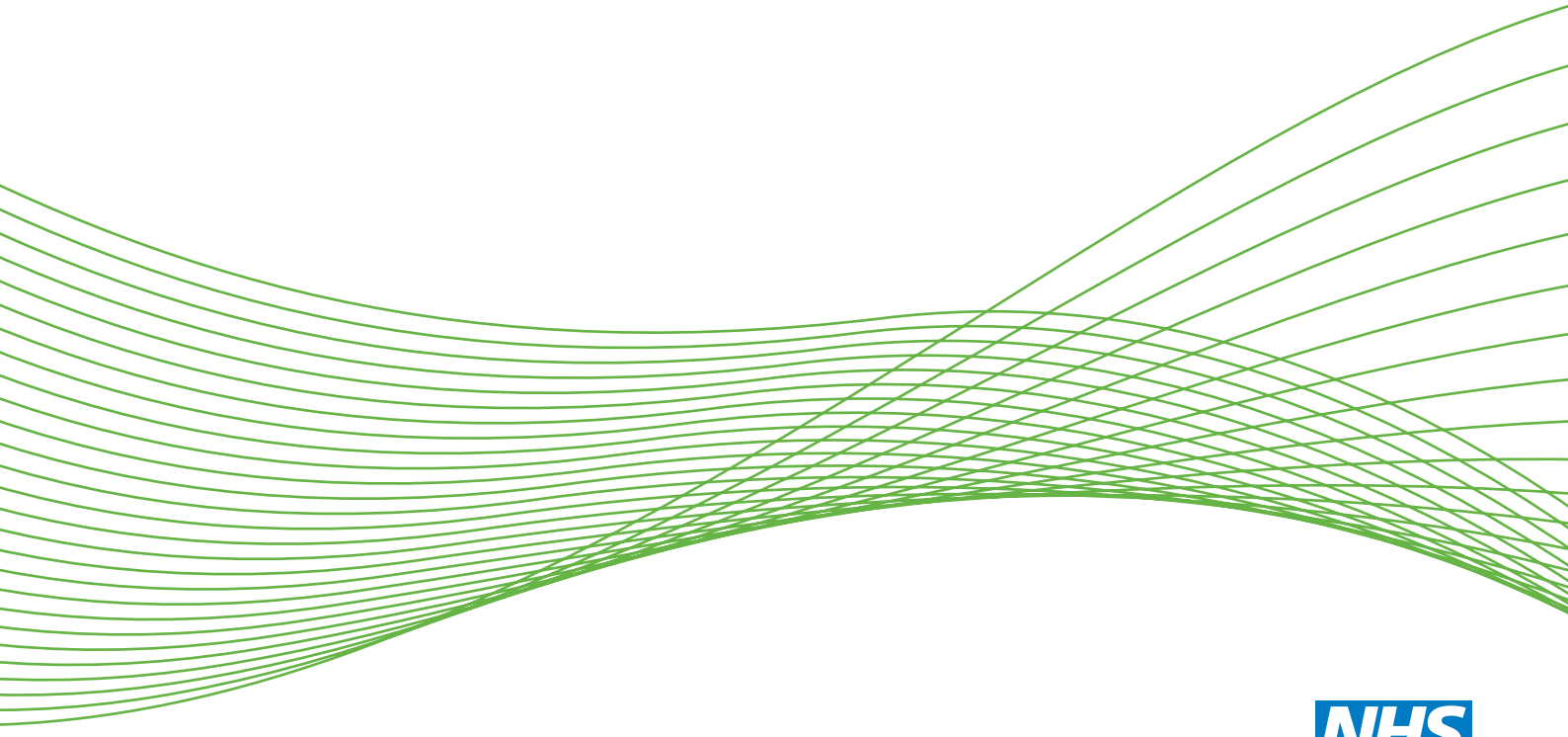

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A randomised placebo-controlled Phase III multicentre trial: low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome (LIPS trial)

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Abstract

A randomised placebo-controlled Phase III multicentre trial: low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome (LIPS trial)

Andreas Goebel,[1]* Jatinder Bisla,[2] Roy Carganillo,[3] Claire Cole,[1] Bernhard Frank,[4] Rima Gupta,[5] Mairi James,[6] Joanna Kelly,[2] Candy McCabe,[7,8] Holly Milligan,[1] Caroline Murphy,[2] Nick Padfield,[3] Ceri Phillips,[9] Helen Poole,[10] Mark Saunders,[11] Mick Serpell,[6] Nick Shenker,[12] Karim Shoukrey,[13] Lynne Wyatt[4] and Gareth Ambler[14]

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Background: Complex regional pain syndrome (CRPS) is a rare, severe post-traumatic pain condition affecting distal limbs. Patients who do not spontaneously improve in 12 months are classed as having 'long-standing CRPS' and often cannot be effectively treated, leading to a poor prognosis. CRPS is associated with functional autoantibodies. Two small trials, including a randomised controlled trial, have suggested that low-dose intravenous immunoglobulin (IVIg) may be an effective treatment for some patients.

Objective: We hypothesised that low-dose IVIg is effective for reducing pain in long-standing CRPS.

Methods: A randomised, double blinded placebo-controlled multicentre trial in seven UK pain management centres. Patients were eligible if they had moderate or severe long-standing CRPS that they had experienced for up to 5 years. Participants were randomly allocated to receive 0.5 g/kg IVIg, the active intervention, or visually indistinguishable 0.1% albumin in saline placebo. Randomisation was initiated by study sites via an independent online randomisation system and was 1 : 1 with varying block sizes, stratified by study centre. Participants, investigators and assessors were blinded to group assignment. The study drug/placebo was infused intravenously at the study centres on day 1 and day 23 after randomisation. The primary outcome was the 24-hour average pain intensity between day 6 and day 42, on an 11-point (0–10) numeric rating scale, compared between the groups. Outcomes were analysed using a mixed-effects regression model that

used 37 measurements of pain intensity (the primary outcome) per participant. All patients who received an infusion and provided any outcome were included in the intention-to-treat analysis.

Results: A total of 111 patients were recruited and assigned between 27 August 2013 and 28 October 2015. Three patients were excluded because they had been inappropriately randomised, five patients were withdrawn from the primary analysis because they provided no outcomes and 103 patients were analysed for the primary outcome. The average pain score in the IVIg group was 0.27 units (95% confidence interval –0.24 to 0.80 units) higher than in the placebo group. Therefore, there is no significant evidence of a treatment effect at the 5% level and there was no significant difference between groups. Six serious adverse events but no suspected unexpected serious adverse reactions were reported during the blinded and open-label phase.

Conclusion and future work: Low-dose immunoglobulin was not effective in relieving pain in patients with moderate to severe CRPS of 1–5 years' duration. Better drug treatments for long-standing CRPS are urgently required.

Trial registration: Current Controlled Trials ISRCTN42179756.

Funding: This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research partnership. Additional funding was obtained by the Pain Relief Foundation. Biotest UK Ltd provided the active study medication at no cost.

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List of abbreviations

AE	adverse event	IVIg	intravenous immunoglobulin
BPI	Brief Pain Inventory	KCT	King's Clinical Trials Unit
CI	confidence interval	MRC	Medical Research Council
CRPS	complex regional pain syndrome	NIHR	National Institute for Health Research
eCRF	electronic case report form	NRS	Numeric Rating Scale
EME	Efficacy and Mechanism Evaluation	QoL	quality of life
EQ-5D	EuroQol-5 Dimensions	RCT	randomised controlled trial
EQ-5D-5L	EuroQol-5 Dimensions, five-level version	SAE	serious adverse event
IgG	immunoglobulin G	TSC	Trial Steering Committee

Plain English summary

Complex regional pain syndrome (CRPS) is a condition that causes persistent severe pain, usually at the site of a previous injury, although pain can affect other parts of the body. CRPS can cause skin around the affected area to become oversensitive to touch.

Although CRPS symptoms can improve or completely resolve, for some people CRPS causes long-term pain. For many of those with moderate to severe CRPS, current pain treatments do not adequately reduce pain.

Exploratory research on a small number of people with moderate to severe CRPS showed that being given intravenous immunoglobulin (IVIg) can reduce pain. IVIg is from blood plasma and contains antibodies that protect against diseases. When people donate blood, the plasma can be separated out. IVIg is given to patients through a vein in their arm.

We conducted a second, much larger, study to see whether or not giving IVIg reduced the pain from CRPS. Participants were randomly assigned to two groups and received two infusions of either IVIg or of placebo (saline solution) 3 weeks apart. Following this, all participants also had the chance to receive two further infusions, at which time they definitely received IVIg. During both parts of the study, participants completed diaries that recorded how much pain they were in on a scale of 1–10.

For the 103 participants in the study, there was no significant difference found in pain reduction between the IVIg and placebo groups. Low-dose IVIg is not an effective treatment for moderate to severe CRPS.

Scientific summary

The text in the *Scientific summary* includes minor additions and formatting changes to the original text as published in Goebel A, Shenker N, Padfield N, Shoudrey K, McCabe C, Serpell M, *et al.* Low-dose intravenous immunoglobulin treatment for complex regional pain syndrome (LIPS): study protocol for a randomized controlled trial. *Trials* 2014;**15**:404.

Background

Complex regional pain syndrome (CRPS) is post-traumatic pain in a limb, and is associated with sensory, motor, autonomic, skin and bone changes. CRPS can resolve spontaneously, but if spontaneous resolution does not occur early, it is less likely to occur later. Many patients with CRPS have no effective method to relieve their ongoing pain. Those patients with CRPS of moderate to severe pain intensity were the target group for this study and report, on average, a very poor quality of life (QoL) and usually cannot work. Immunoglobulin treatment for chronic pain is a novel technology [Goebel A. Immunoglobulin responsive chronic pain. *J Clin Immunol* 2010;**30**(Suppl. 1):103–8]. In a first, open trial we found that low-dose intravenous immunoglobulin (IVIg) may be effective in reducing pain for some patients with CRPS ($n = 11$ participants; $n = 3$ had > 70% pain relief, $n = 2$ had > 25% < 70%, and $n = 6$ had 0–25% relief, following a variable number of low-dose infusion repeats). We later showed that, in one patient, repeat treatments provided reproducible effects. In a UK single-centre crossover randomised placebo controlled trial, a single, low-dose (0.5 g/kg) infusion of IVIg significantly reduced pain in patients with CRPS [$n = 13$, pain intensity on a validated 11-point Numeric Rating Scale (NRS) higher than 4 points (0 = no pain, 10 = pain as bad as you can imagine (Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, *et al.* Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;**113**:9–19)]; these patients had the disease for between 0.5 and 2.5 years. The treatment difference was 1.55 NRS points [95% confidence interval (CI) 1.29 to 1.82 points; $p < 0.001$]. In a responder analysis (12 patients had received treatment), three patients had ≥ 50% less pain (4.5, 5 and 5 NRS points) after IVIg when compared with after saline treatment, and two patients had 29% and 31% less pain (2 and 2.5 NRS points less pain). One patient had 25% less pain (2 NRS points less pain) after saline than those patients having IVIg treatment. The average effect duration was 5 weeks. There was also a significant overall reduction of CRPS-related, non-painful symptoms and, in responders, improved sleep and global improvement, with few adverse events (headaches and pain increases for < 3 days). Post-infusion questionnaires showed successful blinding of patients and study doctors.

The above evidence provided proof of concept for the efficacy of low-dose immunoglobulin treatment for moderate and severe CRPS in reducing pain, with an advantageous side effect profile. The data also suggested that this treatment may improve QoL and pain interference. Because the numbers of treated patients were small, and most research was conducted in a single centre, it was important to confirm these findings in a larger group of patients and across several centres to gain confidence about both efficacy and affect size of this novel technology, and to demonstrate its generalisability.

Objectives

The primary objective was to gain, within 44 months, both definite proof of the clinical efficacy and a more confident estimate of the effect size of low-dose IVIg treatment to reduce pain in patients with moderate or severe CRPS.

Secondary objectives

To achieve better understanding of this technology, including:

- stability of effect with repeat administration
- factors predicting a beneficial response
- effects on additional outcome parameters including stimulus evoked pain, pain interference, QoL and short-term risk profile
- health economics evaluation
- creation of a bank of biological samples at the University of Liverpool for future CRPS serum autoantibody and serum substances research.

Methods (design/study population/participants/consent/randomisation/interventions/outcome measures)

We conducted a multicentre, randomised, double-blind, placebo-controlled, parallel group trial with an open extension across seven UK pain management centres. Patients were eligible if they had moderate or severe long-standing CRPS that they had experienced for up to 5 years. Participants were randomly allocated to receive 0.5 g/kg IVIg, the active intervention, or visually indistinguishable 0.1% albumin in saline placebo. Randomisation was initiated by study sites via an independent online randomisation system, and was 1 : 1 with varying block sizes, stratified by study centre. Participants, investigators and assessors were blinded to group assignment. The study drug/placebo was infused intravenously at the study centres on day 1 and day 22 after randomisation. The primary outcome was the 24-hour average pain intensity between day 6 and day 42, on an 11-point (0–10) NRS, compared between the groups. All patients who received an infusion and provided any outcome were included into the intention-to-treat analysis.

Results

A total of 111 patients were recruited and assigned between 27 August 2013 and 28 October 2015. Three patients were excluded because they had been inappropriately randomised, five patients were withdrawn from the primary analysis because they provided no outcomes and 103 patients were analysed for the primary outcome. The average pain score in the IVIg group was 0.27 units (95% CI –0.24 to 0.80 units) higher than in the placebo group. The 95% CI includes 0 and the corresponding *p*-value is relatively large ($p = 0.30$). Therefore, there is no significant evidence of a treatment effect at the 5% level and there was no significant difference between groups.

Limitations

Patients who had the disease for < 1 year and > 5 years were excluded from the study. Dosing was limited to a low-dose IVIg infusion at 0.5 g/kg. A second active arm with high-dose treatment would have been desirable.

Conclusions and recommendation for research

Low-dose immunoglobulin was not effective in relieving pain in patients with moderate to severe CRPS of 1–5 years' duration. Better drug treatments for long-standing CRPS are urgently required.

Trial registration

This trial is registered as ISRCTN42179756.

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research partnership. Additional funding was obtained by the Pain Relief Foundation. The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. Biotest UK Ltd provided the active study medication at no cost but had no other input into the design or implementation of the study and did not participate in the preparation of this publication.

Chapter 1 Introduction

Background

Complex regional pain syndrome (CRPS) is post-traumatic pain in a limb and is associated with sensory, motor, autonomic, skin and bone changes.[2,3] CRPS can resolve spontaneously, but if spontaneous resolution does not occur early, it is less likely to occur later. Many patients with CRPS have no effective method to relieve their ongoing pain.[4] Those patients with CRPS of moderate to severe pain intensity were the target group for this study and report, on average, a very poor quality of life (QoL) and they usually cannot work.[5]

Immunoglobulin treatment for chronic pain is a novel technology.[6] In a first, open trial we found that low-dose intravenous immunoglobulin (IVIg) may be effective for relieving pain in some patients with CRPS (11 participants: 3 had > 70% pain relief, 2 had > 25%< 70%, and 6 had 0–25% relief, following a variable number of low-dose infusion repeats).[7] We later showed that, in one patient, repeat treatments provided reproducible effects.[8] In a UK single-centre crossover randomised placebo-controlled trial,[9] a single, low-dose (0.5 g/kg) infusion of IVIg significantly reduced pain in patients with CRPS ($n = 13$, pain intensity on an validated 11-point Numeric Rating Scale (NRS) higher than 4 (NRS 0 = no pain, 10 = pain as bad as you can imagine[10]); these patients had the disease for between 0.5 and 2.5 years. The treatment difference was 1.55 NRS points [95% confidence interval (CI) 1.29 to 1.82 points; $p < 0.001$]. In a responder analysis (12 patients had received treatment), three patients had ≥ 50% less pain (4.5, 5 and 5 NRS points) after IVIg when compared with after saline treatment, and two patients had 29% and 31% less pain (2 and 2.5 NRS points less pain). One patient had 25% less pain (2 NRS points less pain) after saline than those patients having IVIg treatment. The average effect duration was 5 weeks. There was also a significant overall reduction of CRPS-related, non-painful symptoms and, in responders, improved sleep and global improvement, with few adverse events (AEs) (headaches and pain increases for < 3 days). Post-infusion questionnaires showed successful blinding of patients and study doctors.

We conducted a trial to explore whether or not subcutaneous immunoglobulin, in weekly self-administration at home, over 1 year would provide sustained pain relief in those who initially responded to 0.5 g/kg IVIg.[8] Five patients with at least 2 NRS points less pain after IVIg in the earlier randomised controlled trial (RCT) were invited to take part. Of these patients, one declined participation and a second patient developed metastasising colon cancer; therefore, three patients participated. By August 2011, two patients who had the disease for 6 years and 5 years at study entry and baseline pain intensities of NRS 7 and 6 points, had experienced sustained pain reduction of > 70% for 12 and 3.5 months, respectively. The third patient, who had had 31% relief in the RCT, showed no benefit. The two responding patients reported major improvement in their QoL; EuroQol-5 Dimensions (EQ-5D) scores[11] improved from 0.26 and 0.30 at baseline to 0.66 and 0.65 at 12/3 months, and both patients experienced reduced interference of daily functioning by their pain [Brief Pain Inventory (BPI)[12] interference scores (pain interference = the impact of pain on activities of daily life) improved from 7.7 and 6.1 at baseline to 1.4 and 0 at 12/3 months].

The aforementioned evidence provides proof of concept for the efficacy of low-dose immunoglobulin treatment for moderate to severe CRPS in reducing pain, with an advantageous side effect profile. The data also suggest that this treatment may improve QoL and pain interference. Because the numbers of treated patients have been small and most research was conducted in a single centre, it was important to confirm these findings in a larger group of patients and across several centres to gain confidence about both efficacy and effect size of this novel technology and to demonstrate its generalisability.

Chapter 2 Objectives

Primary objective

To gain, within 44 months, definite proof of the clinical efficacy and a more confident estimate of the effect size of low-dose IVIg treatment to reduce pain in patients with moderate or severe CRPS.

Secondary objectives

To achieve better understanding of this technology, including:

- stability of effect with repeat administration
- factors predicting a beneficial response
- effects on additional outcome parameters including stimulus evoked pain, pain interference, QoL and short-term risk profile
- health economics evaluation
- creation of a bank of biological samples at the University of Liverpool for future CRPS serum autoantibody and serum substances research.

Chapter 3 Methods

Study design and participants

The LIPS is a Phase II multicentre, randomised, double-blind, placebo-controlled, parallel group trial with an open extension. The open extension was an optional trial element, in which participants who had completed the parallel, blinded phase could receive one or two doses of IVIg. This open-label extension was included to account for the participant's preferences and optimise recruitment and retention rates.

Patients were given the patient information sheet (see *Appendix 1*) to read at least 24 hours before the screening visit, at which time they provided informed consent (see *Appendix 2*).

Eligible patients had moderate or severe CRPS of between 1 and 5 years' duration. A mean pain intensity of ≥ 5 on an 11-point (0–10) NRS over the first seven daily entries after screening and a recorded pain intensity during this period that did not drop below 4 were required for eligibility.

The protocol has been published previously.[1]

Eligibility criteria

Inclusion criteria

- Diagnosis of CRPS I or II according to Budapest research criteria[13] (see *Appendix 3*).
- Duration of the disease of between 1 and 5 years and a mean pain intensity of ≥ 5 on an 11-point (0–10) NRS over the first seven daily entries after screening (the first entry is the day after the screening visit), and a recorded pain intensity that never drops below four during this period, is required for eligibility. At least six out of seven entries of an average of 24 hours of pain intensity are required in the pain diaries.
- Failure to respond (poor efficacy or unacceptable side effects) to drugs recommended for the treatment of neuropathic pain,[14] including pregabalin or gabapentin, a tricyclic antidepressant, and mild and strong opioids (when not contraindicated or refused by the patient).
- Previous specialised pain physiotherapy[15] (when not contraindicated or refused by the patient).
- Willingness to confirm the use of adequate birth control while on the trial in the case of premenopausal women without evidence for an inability to become pregnant.
- Willingness to not start any other treatment for CRPS during the parallel part of the trial.
- Aged ≥ 18 years.

Exclusion criteria

Any individuals meeting any of the following were excluded from the study:

- Other significant chronic pains that, in the view of the study doctor, may make assessment of the pain arising from CRPS difficult.
- Recent initiation of a new therapy for CRPS that, in the view of the study doctor, may change the patient's pain level during the period of participation in the trial.
- Unstable medical conditions.
- Litigation. Patients in litigation will be excluded only if conclusion of that litigation is imminent during the course of the study.
- Pregnant or breastfeeding patients.
- Complete immunoglobulin A deficiency.

- Rare contraindications to IVIg therapy as per summary of product characteristics.
- Receiving IVIg for other reasons.
- Previous enrolment in CRPS IVIg/subcutaneous immunoglobulin trials.
- Ongoing drug or alcohol abuse.
- Psychiatric or mental health disorder that could, in the judgement of the site investigator, interfere with successful study participation.
- Unwillingness or inability to complete daily diaries, or inability to understand the questionnaires being used.
- Cancer other than basal cell carcinoma within the last 5 years. However, those patients who have received definitive treatment, such as curative surgery, > 6 months ago with no known recurrence can be included.
- A history of hypercoagulable or thrombophilic clotting abnormalities.
- A history of thrombembolic events: ischaemic stroke, confirmed myocardial infarction, pulmonary embolism, deep-vein thrombosis except when immobility related (e.g. after injury or operation).
- Unstable angina.
- Renal failure or serum creatinine > 1.5 times the upper limit of normal at screening.
- Any medical condition that, in the opinion of the investigator, would make it unsafe for the patient to participate or that would interfere with assessment of the outcome measures.
- Participation in another interventional trial within 3 months of randomisation. Participation in non-interventional studies is not a reason for exclusion.

The study time frame was scheduled with the date of randomisation defined as day 0 and a screening visit was conducted maximally 3 weeks before this (day –21). Patients received blinded infusions on days 1 and 22. Participants who decided to receive open-label infusions received infusions on days 43 and 64. Paper diaries documenting the patients' self-reported daily pain score were completed from day 2 to day 43 and a weekly pain score was documented for a further 9 weeks to explore the duration of drug and unspecific treatment effects. Participants who received open-label infusions documented a daily pain score to the point of the final infusion they received (1 or 2 open-label infusions) and a weekly pain score 9 weeks thereafter.

Participating centres and recruitment dates

The study was conducted across seven UK-based specialist secondary care pain clinics, and participants were recruited from these clinics or were referred to the clinics from a UK network of pain clinics or patient identification centres. Recruitment commenced in August 2013 at the lead centre and a delay in contract negotiations at a number of recruiting centres resulted in an initial slower-than-anticipated rate of recruitment. However, recruitment targets were met within the 24th month of the project and recruitment was ahead of target by the 27th month of the project. This resulted in the trial over-recruiting and the ending of recruitment 1 month ahead of the study schedule.

The seven centres involved in the multicentre study and dates of active recruitment were:

- The Walton Centre NHS Foundation Trust, Liverpool, UK (August 2013 to October 2015)
- Guy's and St Thomas's NHS Foundation Trust, London, UK (January 2014 to September 2015)
- Royal National Hospital for Rheumatic Diseases, Bath, UK, and University West of England, Bristol, UK (May 2014 to October 2015)
- Queen Elizabeth University Hospital, Glasgow, UK (January 2014 to September 2015)
- Norwich and Norfolk University NHS Trust, Norwich, UK (March 2014 to September 2015)
- Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK (March 2014 to July 2015)
- University Hospital of Leicester NHS Trust, Leicester, UK (April 2014 to June 2015).

The following patient identification centres were set up to refer potential participants to the seven study centres.

- King's College London NHS Foundation Trust, London, UK.
- Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK.
- Royal National Orthopaedic Hospital NHS Trust, Stanmore, UK.
- Royal Devon and Exeter NHS Foundation Trust, Exeter, UK.
- Plymouth Hospitals NHS Trust, Plymouth, UK.
- University Hospitals Southampton NHS Foundation Trust, Southampton, UK.
- City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK.
- The Dudley Group NHS Foundation Trust, Dudley, UK.
- Tameside Hospital NHS Foundation Trust, Tameside, UK.

Interventions

A full description of the assessments utilised in the trial is documented in the published study protocol.[1] The visit schedule and assessments conducted are outlined in *Table 1* and summarised below.

The experimental intervention was 0.5 g/kg Intratect TM IVIg infusion, in combination with ongoing normal standard treatment for CRPS.

Interventions were available in 5 g/100 ml and 10 g/200 ml bottles of Intratect™ IVIg infusion (active) or matching placebo. The volume prescribed was within normal clinical doses per unit weight determined (see *Appendix 4*).

Participants were scheduled to receive infusion of the active or matching placebo on day 1 post randomisation and day 22 post randomisation. The protocol allowed for up to 5 working days from randomisation to the first infusion to account for exceptional circumstances, such as the participant presenting with symptoms that made it unsafe for them to receive the infusion.

Participants who consented to the open-label extension phase received the IVIg on days 43 and 64 post randomisation. The protocol allowed for infusions to occur –1/+1 day from the scheduled date. However, primary outcome timelines remained fixed from the date of randomisation regardless of when the infusion was received. These intervals of 3 weeks between infusions were scheduled in line with usual clinical practice, which accommodates the half-life of IVIg of about 3 weeks.

Safety bloods were collected at the screening visit as part of the eligibility criteria. When consent was provided, additional research bloods were taken at screening and on day 64. CRPS-specific assessments including Limb Assessments and Quantitative Sensory Assessments, vital signs and pregnancy tests were conducted and questionnaires were completed by the participant at set infusion time points, and the paper pain score diaries were retrieved and distributed. Participants who agreed to the open-label extension and received a second infusion were requested to return their daily pain diary and weekly diary to the study team via post. Study staff contacted participants twice following each infusion to confirm adherence to the pain questionnaires and to document any AEs experienced.

All data were collected on trial-specific source data worksheets and transcribed onto electronic case report forms (eCRFs) by authorised trial staff. The eCRF was designed within the Elsevier InferMed MACRO (version 4; Elsevier, London, UK) system which is regulatory compliant (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use *Guideline for Good Clinical Practice*,[16] US Food and Drug Administration 21 CRF Part 11,[17] European Commission Clinical Trial Directive[18]). The eCRF was created in collaboration with the trial statisticians and the investigators, and maintained by the King's Clinical Trials Unit (KCT). It was hosted on a dedicated secure server within King's College London.

TABLE 1 Table of events: summary of study procedures

Study week/month	Visit 1: screen (day –21 to day –10)	Telephone to confirm eligibility (day –11 to day –1)	Day 0 Randomisation	Day 1 Visit 2 (first blinded infusion)	Day 2 (+ up to 3 day) Telephone	Day 5 (+/– 2 days) Telephone	Day 22 (+/– 1 day) Visit 3 (second blinded infusion)	Day 23 (+ up to 3 days) Telephone	Day 26 (+/– 2 days) Telephone	Day 43 (+/– 1 day) Visit 4 (obligatory, with optional first open infusion)	Day 64 (+/– 1 day) Visit 5 (this visit is only for second open infusion)	Day 85 (+ up to 3 days) Telephone	Day 148 (+/– 1 day) Telephone: end of trial	Withdrawal
Registration/ demographics	✗													
Informed consent	✗													
Eligibility form	✗													
Randomisation form			✗											
Medical history	✗													
CRPS history	✗													
Limb examination	✗			✗			✗			✗				
Limb temperature, limb volume	✗									✗				
Safety bloods (U&E, FBC, serum-Ig, LFT)	✗													
Pregnancy test (beta HCG)	✗													
Pregnancy test (urine)										✗				
Screening pain diaries (average 24-hour pain intensity only)	[a]	✗ (over telephone)		[b]										
Detailed (blind) diary, weeks 1–3 (average pain intensity, pain unpleasantness, sleep quality). Patients who consent will receive daily prompting text reminders during days 2–42				[a]			[b]							

Study week/month	Visit 1: screen (day –21 to day –10)	Telephone to confirm eligibility (day –11 to day –1)	Day 0 Randomisation	Day 1 Visit 2 (first blinded infusion)	Day 2 (+ up to 3 day) Telephone	Day 5 (+/– 2 days) Telephone	Day 22 (+/– 1 day) Visit 3 (second blinded infusion)	Day 23 (+ up to 3 days) Telephone	Day 26 (+/– 2 days) Telephone	Day 43 (+/– 1 day) Visit 4 (obligatory, with optional first open infusion)	Day 64 (+/– 1 day) Visit 5 (this visit is only for second open infusion)	Day 85 (+ up to 3 days) Telephone	Day 148 (+/– 1 day) Telephone: end of trial	Withdrawal
Detailed (blind) diary, weeks 4–6 (average pain intensity, pain unpleasantness, sleep quality). Patients who consent will receive daily prompting text reminders during days 2–42							[a]			[b]				
Detailed (open) diary, weeks 7–9 (average pain intensity, pain unpleasantness, sleep quality). For patients who receive open-label infusion only										[a]	[b]			
LIPS detailed (open) dairy, weeks 10–12 (average pain intensity, pain unpleasantness, sleep quality). For patients who receive open-label infusion only											[a]	[c]		
Simplified pain diaries (weekly pain intensity scores only)										[a] (patients who do not receive open-label infusion)	[c] (patients who do not receive open infusion)	[a] (patients who do receive open infusions)	[c] (patients who do receive open infusions)	[a]
Questionnaires														
Expectation from treatment				✗										
EQ-5D-5L	✗						✗			✗				

continued

TABLE 1 Table of events: summary of study procedures (*continued*)

Study week/month	Visit 1: screen (day –21 to day –10)	Telephone to confirm eligibility (day –11 to day –1)	Day 0 Randomisation	Day 1 Visit 2 (first blinded infusion)	Day 2 (+ up to 3 day) Telephone	Day 5 (+/– 2 days) Telephone	Day 22 (+/– 1 day) Visit 3 (second blinded infusion)	Day 23 (+ up to 3 days) Telephone	Day 26 (+/– 2 days) Telephone	Day 43 (+/– 1 day) Visit 4 (obligatory, with optional first open infusion)	Day 64 (+/– 1 day) Visit 5 (this visit is only for second open infusion)	Day 85 (+ up to 3 days) Telephone	Day 148 (+/– 1 day) Telephone: end of trial	Withdrawal
McGill Pain Questionnaire (Short Form) pain descriptors	✗						✗			✗				
BPI	✗						✗			✗				
HADS	✗						✗			✗				
Pain catastrophising (Sullivan's catastrophising scale)	✗						✗			✗				
Global Impression of Change Scale							✗			✗	✗		✗	
Health/social care utilisation	✗													
Patient-developed measures	✗						✗			✗				
Stanford Presenteeism Scale	✗									✗				
Neglect-like symptoms	✗									✗				
Vital signs (pulse, blood pressure, before and after infusion)				✗			✗			✗	✗			
Treatment infusion administration				✗			✗			✗	✗			
Research bloods (30 ml)	✗									✗				
Quantitative sensory testing (subset of 40 patients only)	✗			✗ (if not done on visit 1)						✗				

Study week/month	Visit 1: screen (day –21 to day –10)	Telephone to confirm eligibility (day –11 to day –1)	Day 0 Randomisation	Day 1 Visit 2 (first blinded infusion)	Day 2 (+ up to 3 day) Telephone	Day 5 (+/– 2 days) Telephone	Day 22 (+/– 1 day) Visit 3 (second blinded infusion)	Day 23 (+ up to 3 days) Telephone	Day 26 (+/– 2 days) Telephone	Day 43 (+/– 1 day) Visit 4 (obligatory, with optional first open infusion)	Day 64 (+/– 1 day) Visit 5 (this visit is only for second open infusion)	Day 85 (+ up to 3 days) Telephone	Day 148 (+/– 1 day) Telephone: end of trial	Withdrawal
Concomitant and CRPS pain treatments medications	✗	✗		✗	✗		✗			✗	✗		✗	✗
Concomitant therapies	✗	✗		✗	✗		✗			✗	✗		✗	✗
AEs form				✗	✗		✗			✗	✗		✗	✗
Patient medication guess				✗	✗		✗							✗
Physician medication guess				✗			✗							✗
Research nurse medication guess				✗			✗							✗
Withdrawal form														✗

EQ-5D-5L, EuroQol-5 Dimensions, five-level version; FBC, full blood count; HADS, Hospital Anxiety and Depression Scale; HCG, Human chorionic gonadotropi6; LFT, liver function test; U&E, urea and electrolytes.

a Day issued to patient.

b Day of collection back from patient.

c Diary returned using prepaid envelope).

A trial manager was employed to conduct onsite/central monitoring of the data and was responsible for raising and resolving queries to ensure quality assurance.

All causes for withdrawal from randomised treatment were reported at days 22 and 43 post randomisation. The prevalences of AEs and reactions were reported descriptively at 22 and 43 days post randomisation. If given open-label infusion, AEs reported from 43 to 85 days post randomisation were tabulated separately for reports rather than being reported with blinded AEs. Serious adverse events (SAEs) were monitored for 21 days after the final dose of IVIg/placebo or until resolution.

The study end was defined as the last participant's final study contact at day 148 for those who consented to receive open-label infusions, or at day 64 for those who declined the open-label extension.

Outcomes

The primary outcome was the average 24-hour pain intensity over 37 days, recorded in paper pain diary entries for the previous 24 hours and collected on days 6 to 42 (day 1 = day of first infusion). The trial initially utilised a text messaging system to collect the NRS pain scores from patients who consented as a supplementary means of gathering the primary outcome data; however, the system was abandoned by agreement of the Trial Steering Committee (TSC) owing to a high compliance rate of the paper diaries being completed and returned. In addition, there was a low response rate of the text message scores sent by patients who had consented to the system and the site staff experienced technical difficulties in setting patients up to use the system.

Secondary outcomes were the pain interference measured using the interference subscale of the BPI[12] and QoL measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L).[19]

All other outcomes were exploratory.

A list of the measures that were used is given below (for measurement times see *Table 1*).

- Detailed daily pain diaries (three items: pain unpleasantness,[10] average 24-hour NRS pain intensity, last 24-hour sleep quality[20]), and simplified weekly (weekly NRS pain intensity) pain diaries.
- AEs.
- BPI[12] (diagram, worst pain intensity and interference scales only).
- Concomitant medications.
- Concomitant therapies.
- Patient weight.
- Skin temperature measured with a surface thermometer.
- Limb volume measured with a water bath technique.
- EQ-5D-5L.[19]
- Expectations from treatment.[21]
- Functional items and fatigue suggested by, and developed together with, patient group (five scales).
- Patient Global Impression of Change.[22]
- Hospital Anxiety and Depression Scale.[23]
- Health and social care utilisation.
- Limb examination recording Budapest CRPS signs and any additional abnormalities on inspection, and sensory (cotton wool, pinprick, cold fork) and motor (observation of active range) examination.
- McGill Pain Questionnaire (Short Form).[24]
- Quantitative sensory testing in 40 patients with stimulus evoked pain, excepting thermosensitivities (only in three trial centres).
- Sullivan's Pain Catastrophising Scale.[25]
- Work interference (Stanford Presenteeism Scale).[26]

- Neglect-like symptoms in CRPS.[27]
- Patient recommended scale (see *Appendix 5*).

Randomisation and blinding

Participants were randomly assigned (1 : 1) to IVIg or placebo by site staff who were authorised to request randomisation via an independent online randomisation system based at the KCT within the Institute of Psychology, Psychiatry and Neuroscience. Allocation was at the level of the individual patient via block randomisation with randomly varying block sizes, stratified by centre.

The trial was double blinded. Supplies of the study medication dispensed on day 1 and day 2 post randomisation were blinded (and the IVIg prescribed on days 43 and 64 was open label). Blinding was achieved by preparing the investigational medicinal product/active and placebo solution (0.1% albumin in normal saline) into bottles of identical appearance, including the labelling and the batch numbers/expiry dates. By adding albumin to the placebo, the solutions were indistinguishable in colour and foaming of the solution. The study drug was delivered to the designated pharmacy contact with a removable section on the bottle and secondary packaging which informed the pharmacy staff of the true contents (active or placebo). This section was removed when dispensing in order to maintain blinding. Study medication was prescribed by an authorised study physician in accordance with the protocol, using a trial-specific prescription.

Blinding was maintained by utilising the services of an external pharmaceutical project management company, ModePharma, which centrally monitored study medication and instructed the distribution of the study medication from the Aseptic Manufacturing Pharmacy Unit at Royal Liverpool and Broodgreen Hospital, Liverpool, UK. With the exception of the pharmacy site staff, the staff at ModePharma and Royal Broadgreen Hospital and the Director of KCT, all other research team members involved in the study were blinded to the treatment allocation. The analysing statistician was subgroup unblinded only until analyses were complete, at which point the trial was fully unblinded.

In the event of an urgent need to unblind the treatment of participants, site staff were informed of the contact details of a code break service that was utilised through Guy's Medical Toxicology Unit. However, the service was not utilised and no participants were unblinded throughout the duration of the trial.

Statistical analysis

The sample size was based on the following assumptions based from the pilot study:[9] 122 participants were required to detect a difference in pain score of 1.2 using a two-sample *t*-test, assuming 5% statistical significance, 85% power and a common standard deviation of 2.2 (as in our previous study[9]). Assuming 10% loss to follow-up and a 5% non-compliance increased this number to 152 participants. We intended to collect 37 measurements of pain intensity (the primary outcome) per participant and analyse the outcome using a mixed-effects regression model. Therefore, the sample size was reduced based on these extra measurements. From the pilot study,[9] the correlation between a patient's measures was assumed to be 0.7; hence the multiplying factor was $[1 + (37 - 1) \times 0.7)/37 = 0.71]$. Therefore the total required sample size was calculated at $152 \times 0.71 = 108$ participants, 54 patients per study arm.[28]

Primary analysis

The primary outcome was analysed using a mixed model to establish any difference between pain scores after IVIg and placebo. The stratification factor (study centres) was a fixed effect. The model efficiently modelled the repeated measurements data. Modelling assumptions were checked (e.g. residuals) and all analyses were performed on an intention-to-treat basis. Every effort was made to reduce loss to follow-up using fixed-point telephone calls. Participants who provided any outcome data were included and no primary outcome were omitted from the primary analysis; however, they were included within a sensitivity

analysis along with participants who were incorrectly consented into the trial for not meeting the inclusion criteria.

Secondary analysis

As a secondary analysis, we calculated the proportion of patients in each arm who achieved 50% or 30% pain relief based on the average pain level entered on day 6–42, compared with their baseline level of pain (the average pain level recorded during the first 7 days of the screening period). Using these proportions, we calculated the number needed to treat with IVIg so that one additional patient will achieve 50% pain relief.

Possible changes in treatment effect over time and association between disease duration, psychological baseline measurements, allergy status/low baseline immunoglobulin G (IgG) plasma level, IgG increase, and treatment response, and any association between psychological measurements with the primary outcome was investigated using exploratory plots and regression models with interaction terms. Change in McGill Pain Questionnaire-Short Form,[24] descriptor terms, limb temperature and quantitative sensory testing changes before and after IVIg or placebo treatments on affected versus/contralateral sides, pain interference and QoL outcomes were investigated using either standard regression models or mixed models. In those who decided to receive both open infusions and who had at least 30% or 2 NRS points average pain relief from 6 to 20 days after their last open infusion compared with baseline, the time between the last open infusion and the first period with average weekly pain equalling or exceeding baseline –1 NRS point was calculated as the IVIg effect duration. As the study ended on day 148 (12 weeks after the second open infusion), later effects were not recorded.

The statistical tests were conducted using Stata® version 14 (StataCorp LP, College Station, TX, USA).

A Data Monitoring Committee was formed, which had access to the unblinded data and monitored the progress of the trial in terms of safety and ethics issues. A blinded interim analysis was performed for futility and safety after half of the patients completed the trial and reported to the TSC that the trial should continue based on pre-agreed stopping rules.

Patient and public involvement

In preparation for the application to the National Institute for Health Research (NIHR), the early design had been sent to several patients with CRPS and comments were integrated. The final study protocol for the full proposal was then sent to 18 patients with CRPS who had previously agreed to be contacted for this purpose. These patients were a subgroup of patient participants in the ‘Liverpool CRPS pathway group’, a regional support group. Responses mostly related to convenience of attendance and additional outcomes, and have been implemented. Further suggestions from a patient participant on the NIHR review board were also taken on board. Patient information sheets were reviewed for acceptability by the same Liverpool patient group, and suggestions were implemented.

A patient representative with a history of CRPS volunteered to join the TSC and regularly attended these meetings. The patient representative offered invaluable advice and guidance throughout the trial.

The plain English summary was also forwarded to our patient representative on the TSC. Minor suggestions raised were addressed prior to submission.

Ethics

The study was approved by the National Research Ethics Service Committee East of England-Hatfield on 6 June 2012 and each site was granted site-specific approval from its NHS Research and Development department before trial commencement. This trial is registered with ISRCTN42179756.

Protocol changes

Original protocol (version 1.1) is dated 2 May 2012 and the final version of the protocol is available online (www.nets.nihr.ac.uk/projects/eme/111433) (*Table 2*).

TABLE 2 Summary of protocol changes

Substantial amendment number	Summary of changes
Substantial amendment 1, protocol version 2.0 (19 October 2012)	**Sponsor contact** The new details reflect a change to the legal representative for one of the sponsors **7.1 Primary outcome measure** The new text describes an extended period for 24-hour pain diary from 15 to 37 days. An additional description of the text prompting system is described to improve compliance This change reverts back to the original design agreed by the funders as the TSC felt it more robust **7.2 Secondary outcome measures** The EQ-5D will now be used as a measure of QoL The rewording clarifies the two parts to the secondary outcomes. The secondary outcomes and the exploratory outcomes. There were additional missing references for the assessments to be used that have now been included. The standard gamble was removed on the advice of a health economist **8.2 Exclusion criteria** Serum IgA levels previously defined as an exclusion criterion have now been redefined An additional exclusion criterion has been included to prevent the inclusion of individuals that have participated in an intervention trial within the past 3 months **9 Screening recruitment and consent** Additional text has been included for clarification **10.3 Selection and timing of dose for each participant** Additional details included to clarify the inclusion of participants that are non-compliant for the infusion visit **10.6 Packaging and labelling of investigational medicinal product** Study name and EudraCT number now included on label **10.11 Concomitant medications** Additional information is provided on how to proceed if there is a change in a participant's condition with regards to CRPS and trial intervention

continued

TABLE 2 Summary of protocol changes (*continued*)

Substantial amendment number	Summary of changes
	10.12.2 Biochemistry Additional tests have been included for biochemistry **11.3 Implementation procedures** Clarification of the implementation procedures, including a checklist for the site nurses to go through before a participant can be randomised **14.1.1 Efficacy safety** Treatment stopping rules agreed and included The reporting of AEs has also been clarified **14.2 Sample size calculation** The sample size calculation was adjusted to account for the increased number of days included for the measurement of the primary outcome This change reverts back to the original design agreed by the funders as the TSC felt it more robust **15.3 Withdrawal of participants** The following points were included to clarify discontinuation of participants in the study **16.2 Monitoring Quality Control and Assurance Safety** Changes have been made to the representatives in the TSC and the DMEC Addition of PI video The video is intended to standardise the explanation of the trial across sites. As the outcome is subjective this is felt to be of importance
Substantial amendment 2, protocol version 3.0 (11 April 2013)	**REC** Updated REC address **7.2 Secondary and exploratory outcome measures** Removal of time-trade-off scale **8.1 Inclusion criteria** Rewording of inclusion criteria 4: previous specialised pain physiotherapy (when not contraindicated or refused by the patient) **10 Study medication** Clarification of drug/placebo availability, drug/placebo labelling and packaging. Changes to the blinding procedure **10.12.3 Pregnancy** Addition of urine pregnancy test at visit 4 for females wanting open-label drug Summary of study procedures Clarification to study procedures PI video Addition of slides

TABLE 2 Summary of protocol changes (*continued*)

Substantial amendment number	Summary of changes
Substantial amendment 3, protocol version 4.0, (1 July 2013)	**7.2 Secondary outcome measures** Neglect-like symptoms in CRPS questionnaire have been added to the list of measures to be used within the secondary and exploratory outcome measures **14 Statistical considerations** Allergy status and low-baseline IgG plasma level have been added to secondary analysis
Substantial amendment 4, protocol version 5.0, (4 October 2013)	Protocol (throughout) Additional site: Leicester Minor corrective changes Participant information sheet Amendment to common, occasional and rare side effect of IVIg
Non-substantial amendment 5, protocol version 5.1 (7 July 2014)	**10.3 Selection and timing of dose for each participant** Clarification of an allowance of 5 working days instead of 5 days for first infusion and inclusion for analysis

DMEC, Data Monitoring and Ethics Committee; EudraCT, European Clinical Trials Database; IgA, immunoglobulin A; PI, principal investigator; REC, Research Ethics Committee.

Chapter 4 Results

In total, 121 participants were screened, of whom 111 participants were randomised to one of the two trial arms. A total of 56 participants were randomised to placebo and 55 to IVIg. Two of these participants did not receive their first infusion and supplied no outcome pain data. Three further participants did receive their first infusion but also did not supply any outcome pain data. Therefore, all five of these participants are excluded from the primary analysis.

In addition, three participants were randomised in error. Two of these participants had an average baseline pain score (over the first 7 days) of < 5 and one participant had the disease for < 12 months. These three participants (all randomised to IVIg) are excluded from the primary analysis.

The primary analysis was performed on 103 participants, with 53 in the placebo group and 50 in the IVIg group. This is summarised in *Figure 1*.

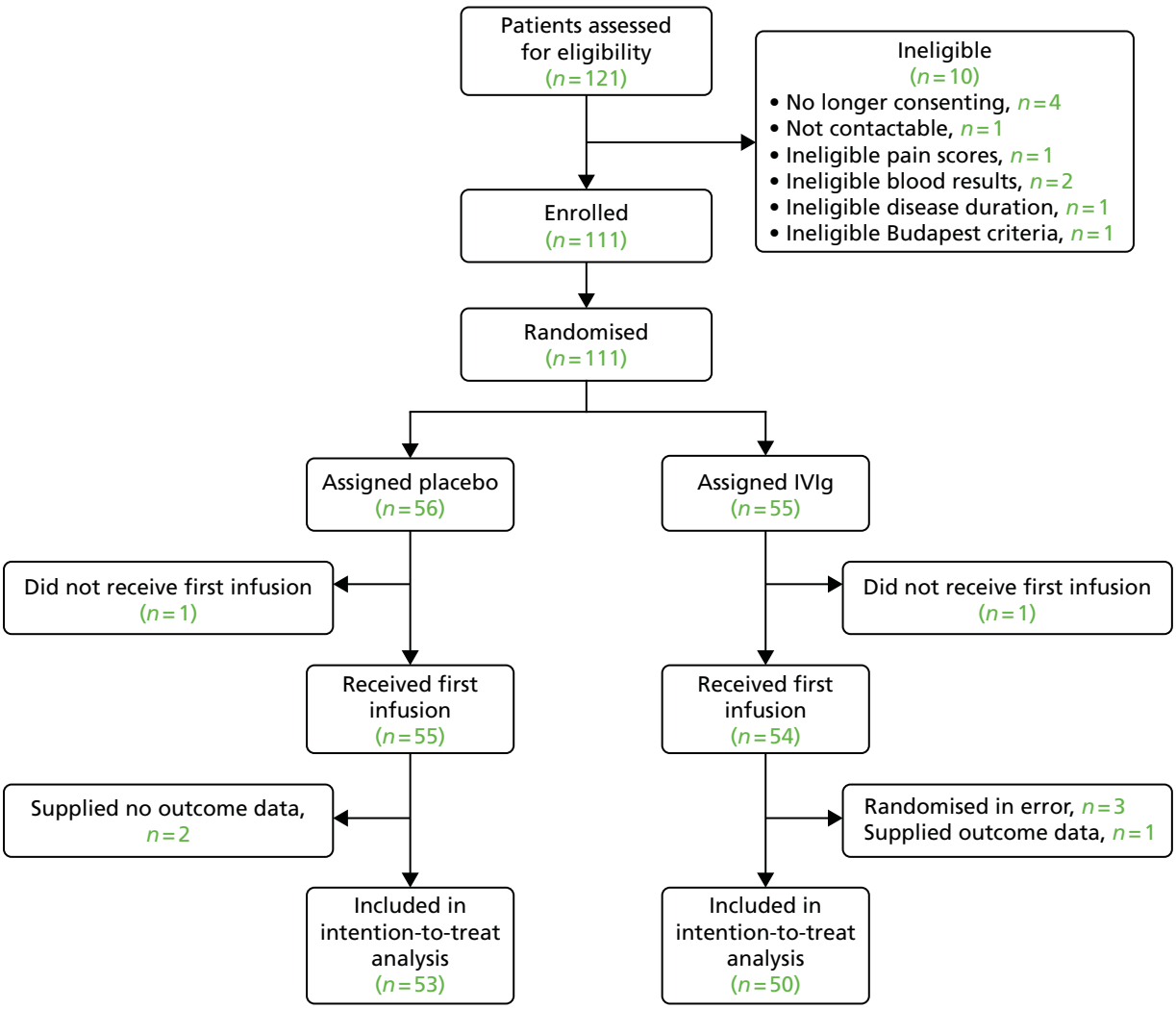

FIGURE 1 Participant flow diagram.

Withdrawals from study medication

Twelve participants withdrew their consent to use the study medication before the end of the blinded phase (day 42). This includes the two participants who did receive their first infusion and the three participants who received their first infusion but did not supply any outcome data. The remaining seven participants received their first infusion and completed their pain diaries for at least 2 weeks and are included in the primary analysis. Only one of these 12 participants received a second infusion. Further details regarding these participants can be found in *Table 3*.

Baseline characteristics

Baseline characteristics for the 111 randomised participants are shown in *Table 4*. It is clear that balance has been achieved for most variables, although there is a slight sex imbalance.

The distribution of age, disease duration and mean baseline pain by trial arm is shown in *Figures 2–4*.

Time to infusion

Time to first infusion is shown in *Table 5* for all randomised participants ($n = 111$). There were seven early and three late infusions. Two participants did not receive their first infusion as detailed earlier.

The protocol states the following: in exceptional circumstances, when a randomised participant does not attend the first infusion on day 1, delay of the first infusion up to 5 working days is acceptable (section 10.3 of protocol). Specifically, one participant did attend their first infusion on day 1 but presented with a high fever and it was not safe to proceed. This participant recovered and had their infusion on day 8 (i.e. a delay of 5 working days).

TABLE 3 Details of withdrawals during blinded phase

Day	Treatment	Reason for withdrawal	First infusion?	Second infusion?
0	Placebo	Refused further participation	No	No
1	IVIg	Participant unable to travel	No	No
6	Placebo	AE (participant withdrew)	Yes	No
15	Placebo	AE (participant withdrew)	Yes	No
20	IVIg	Other (alternative treatment sought: high-dose capsaicin patch)	Yes	No
20	IVIg	Participant unable to travel	Yes	No
21	IVIg	Refused further participation	Yes	No
21	IVIg	AE (participant withdrew)	Yes	No
22	Placebo	AE (team withdrew)	Yes	No
22	IVIg	AE (team withdrew)	Yes	No
33	IVIg	Refused further participation	Yes	No
36	IVIg	AE (participant withdrew)	Yes	Yes

Shaded rows correspond to participants excluded from the primary analysis.

TABLE 4 Baseline characteristics by trial arm for all randomised participants ($n = 111$). Values are either mean (SD) or number (%)

	Trial arm	
	Placebo ($n = 56$)	IVIg ($n = 55$)
Age (years)	41.0 (12.5)	43.7 (11.6)
Sex (female)	42 (75.0%)	35 (63.6%)
Ethnicity		
Asian	0 (0.0%)	2 (3.6%)
White	55 (98.2%)	53 (96.4%)
Other	1 (1.8%)	0 (0.0%)
Disease duration (years)	2.5 (1.2)	2.3 (1.2)
CRPS type		
I	49 (87.5%)	47 (85.5%)
II	6 (10.7%)	6 (10.9%)
Undecided	1 (1.8%)	2 (3.6%)
Average baseline pain	7.40 (1.10)	7.43 (1.13)
Site		
Bath	4 (7.1%)	6 (10.9%)
Cambridge	5 (8.9%)	4 (7.3%)
Glasgow	9 (16.1%)	9 (16.4%)
Leicester	3 (5.4%)	3 (5.5%)
Liverpool	16 (28.6%)	15 (27.3%)
London	14 (25.0%)	14 (25.5%)
Norwich	5 (8.9%)	4 (7.3%)

SD, standard deviation.

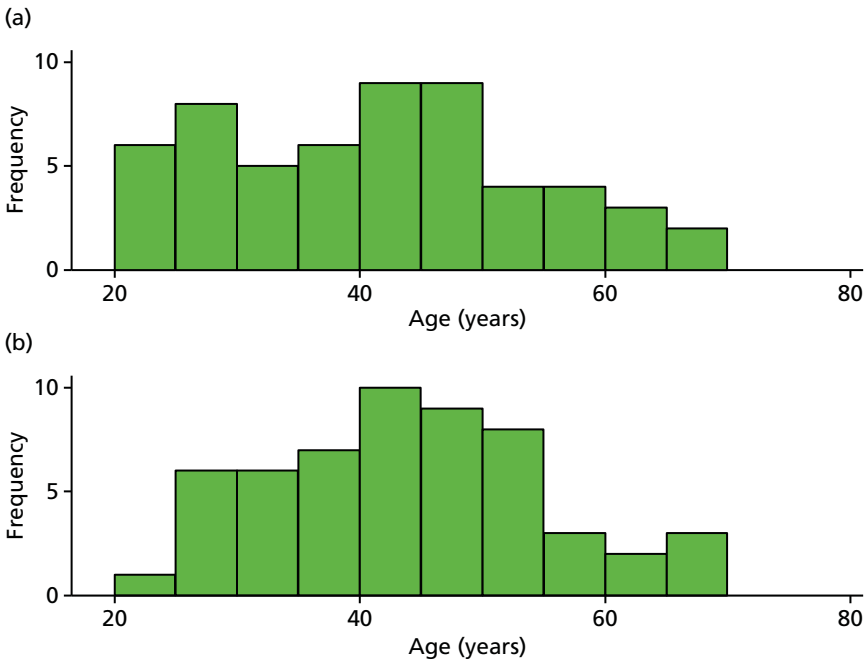

FIGURE 2 Distribution of age by trial arm. (a) Placebo and (b) IVIg.

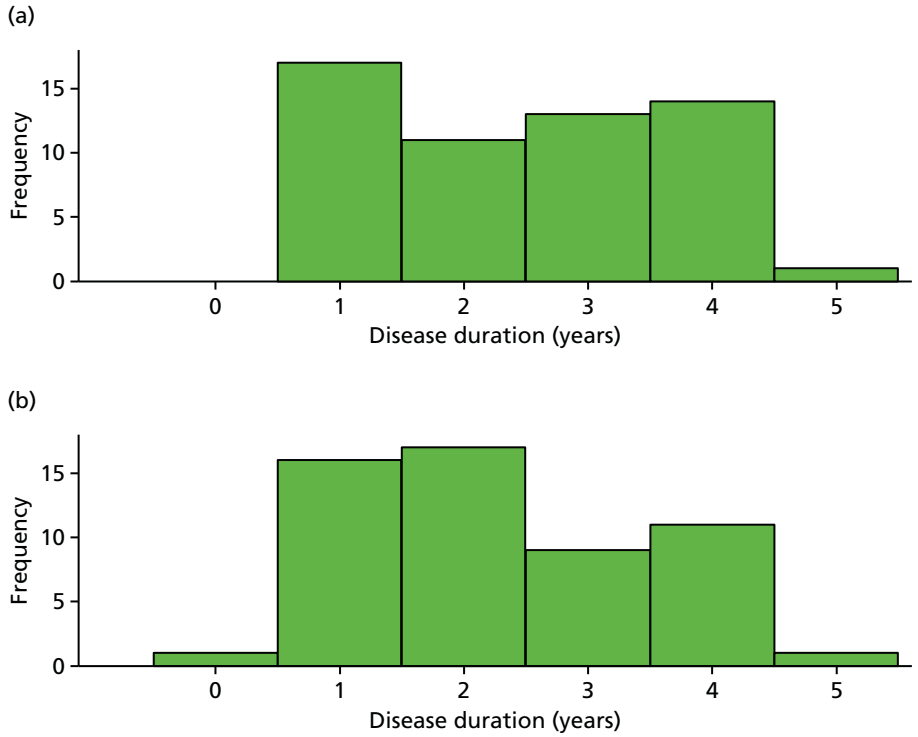

FIGURE 3 Distribution of disease duration by trial arm. (a) Placebo and (b) IVIg.

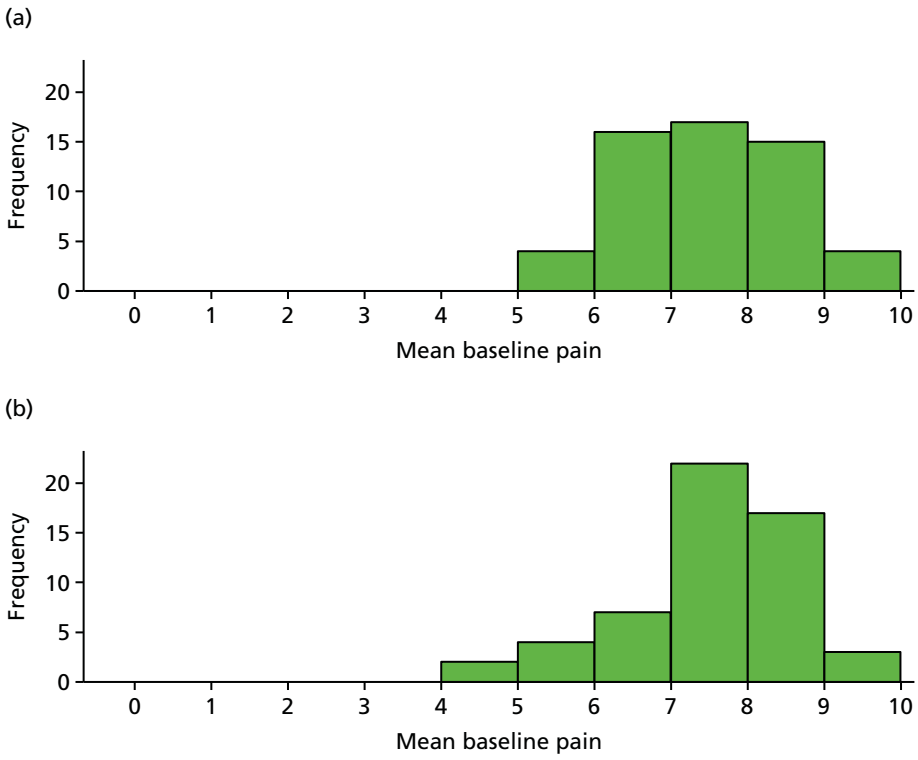

FIGURE 4 Distribution of average baseline pain by trial arm. (a) Placebo and (b) IVIg.

TABLE 5 Time to first infusion by trial arm

	Trial arm	
	Placebo	IVIg
Time to first infusion (days)		
0	6	1
1	48	51
4	1	–
7	–	1
8	–	1
(No infusion)	1	1
Total	56	55

One participant was randomised 12 days too early owing to a site administrative error. The TSC was consulted and it was agreed that their randomisation date could be 'corrected'.

Table 6 shows the time to second infusion for all randomised participants ($n = 111$). Most infusions were administered between days 21 and 23, although there were four infusions later than this. Eleven participants withdrew from treatment medication and did not receive a second infusion.

Participant follow-up (blinded phase: days 6–42)

Table 7 shows the number of (non-missing) recorded pain scores for each participant. Only five participants produced no outcome pain score data as detailed earlier. All other participants recorded at least 14 values.

Primary analysis ($n = 103$)

Average pain scores (over days 6–42) for each participant, by trial arm, are shown in *Figure 5* for the 103 participants included in the primary analysis. It is clear that the pain scores are very similar for each group.

Fitting the primary analysis mixed model produced the treatment effect estimate in *Table 8*. The average pain score in the IVIg group was 0.27 units (95% CI –0.24 to 0.80 units) higher than in the placebo group. The 95% CI includes 0 and the corresponding p-value is relatively large ($p = 0.30$). Therefore, there is no significant evidence of a treatment effect at the 5% level. The full model results and residual plots are shown in *Table 9* and *Figure 6*.

As a check, a t-test was used to compare the mean pain scores across trial arms. This produced a treatment effect of 0.28 ($p = 0.30$), which, as expected, is very similar to that from the primary analysis. The mixed model was also refitted with an analysis of covariance adjustment for average baseline pain. This produced a treatment effect of 0.23 ($p = 0.22$), which, again, is similar to that of the primary analysis.

One participant recorded very low pain scores (mean pain = 0.9 from 37 measurements). Omitting this participant from the primary analysis reduces the placebo treatment effect by one-third (to 0.17).

TABLE 6 Time to second infusion by trial arm

	Trial arm	
	Placebo	IVIg
Time to second infusion (days)		
21	6	5
22	40	33
23	4	8
24	–	1
26	1	–
29	–	1
36	1	–
(No infusion)	4	7
Total	56	55

TABLE 7 Number of completed pain scores (days 6–42) for each participant by trial arm

	Trial arm	
	Placebo	IVIg
Number of recorded pain scores		
14	–	1
15	–	1
16	2	1
17	–	2
19	–	1
34	–	1
35	1	1
36	9	5
37	41	40
(None)	3	2
Total	56	55

Absolute pain reduction

The difference between average pain score and average baseline pain score is plotted for each participant in *Figure 7*. These differences are also summarised in *Table 10*.

Percentage pain reduction

Average pain scores were also plotted against average baseline pain scores. The outlying participant (average pain = 0.9) has been removed from *Figure 8* for clarity.

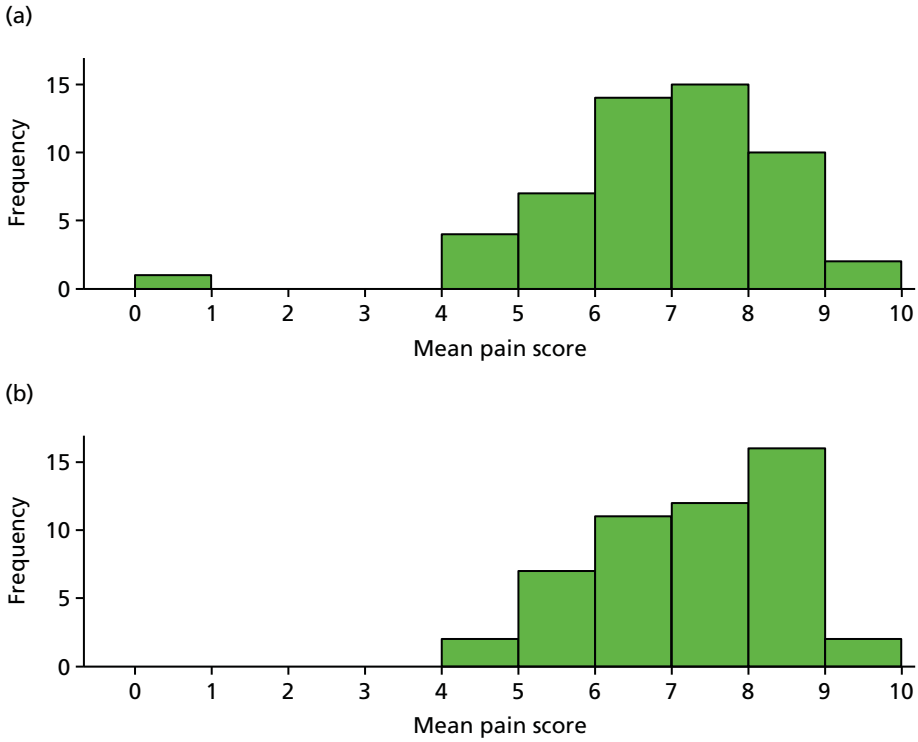

FIGURE 5 Average pain score for each participant by trial arm. (a) Placebo and (b) IVIg.

TABLE 8 Treatment effect from primary analysis

Variable	Coefficient (95% CI)	*p*-value
Average pain (IVIg – placebo)	0.27 (–0.25 to 0.80)	0.30

TABLE 9 Full results for mixed model

Variable	Coefficient (95% CI)	*p*-value
Average pain (IVIg – placebo)	0.27 (–0.25 to 0.80)	0.30
Site (Cambridge)	0.06 (–1.22 to 1.34)	0.88
Site (Glasgow)	0.14 (–0.94 to 1.23)	
Site (Leicester)	0.07 (–1.32 to 1.46)	
Site (Liverpool)	–0.38 (–1.38 to 0.63)	
Site (London)	0.03 (–0.99 to 1.05)	
Site (Norwich)	–0.24 (–1.63 to 1.15)	
Intercept	6.99 (6.07 to 7.92)	< 0.001
σ_u	1.33 (1.16 to 1.53)	
σ_2	1.08 (1.05 to 1.10)	

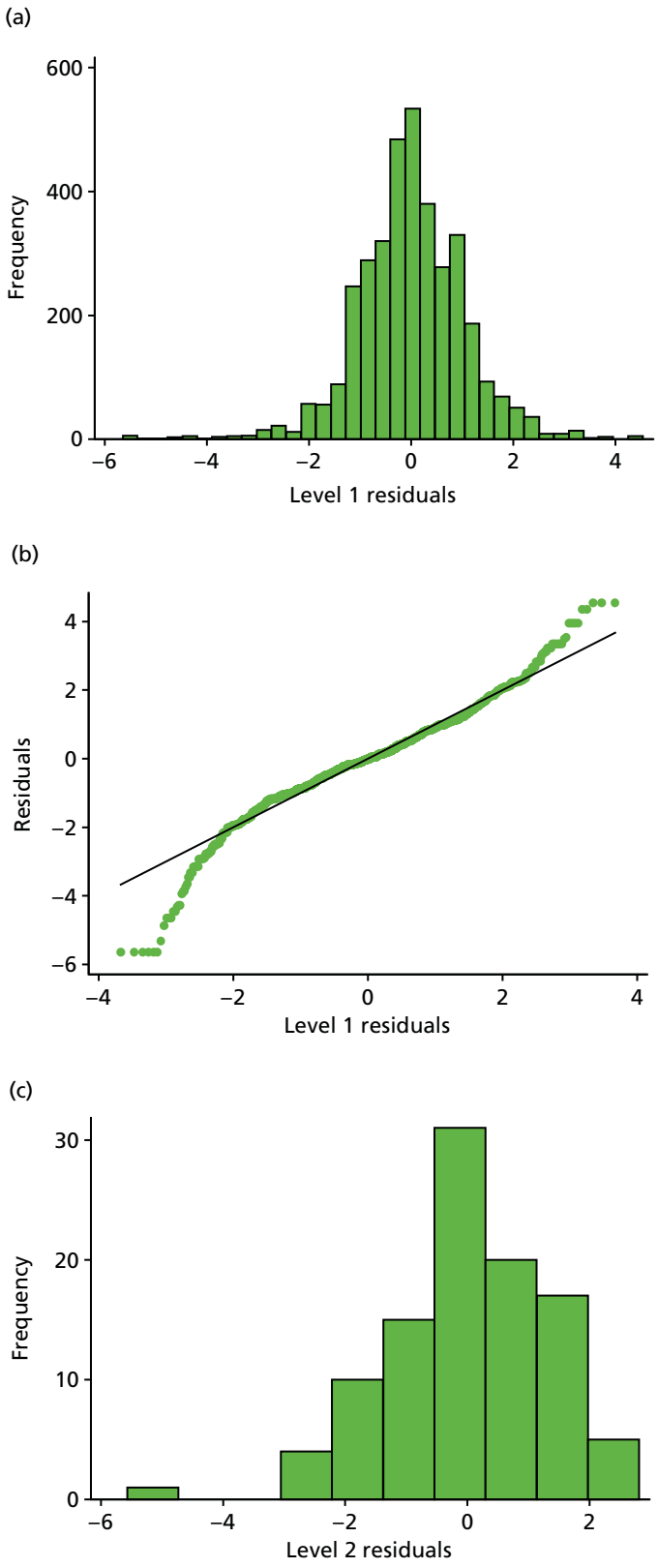

FIGURE 6 Histogram and normal plots for the level 1 (measurements) and 2 (participant) residuals. (a) Level 1 residual histogram; (b) level 1 residual normal plot; (c) level 2 residual histogram; and (d) level 2 residual normal plot. (*continued*)

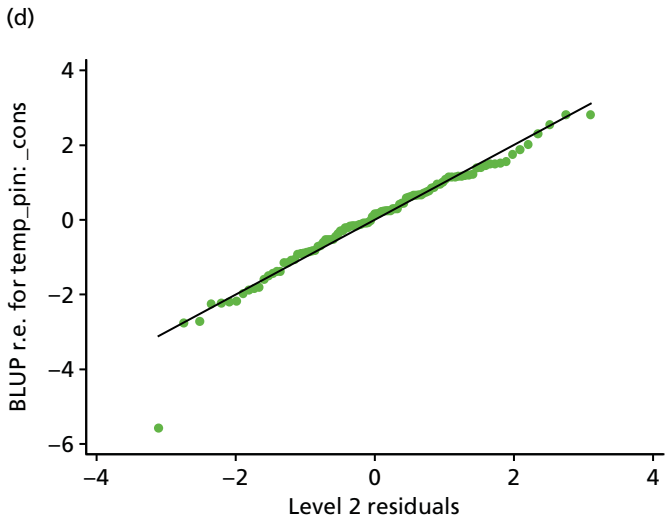

FIGURE 6 Histogram and normal plots for the level 1 (measurements) and 2 (participant) residuals. (a) Level 1 residual histogram; (b) level 1 residual normal plot; (c) level 2 residual histogram; and (d) level 2 residual normal plot.

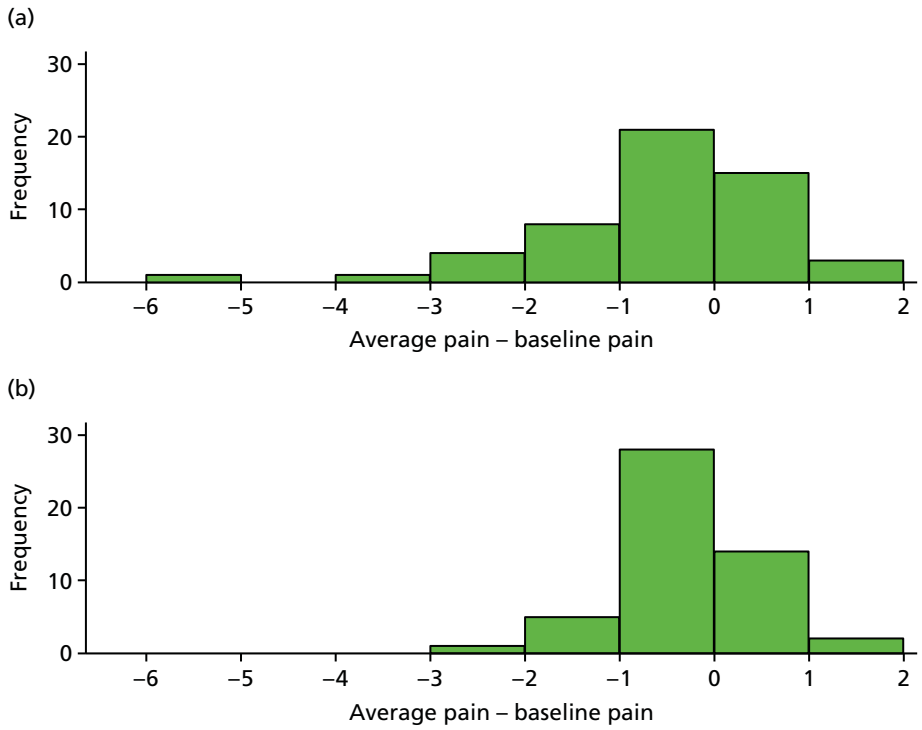

FIGURE 7 Difference between average pain and average baseline pain for each participant. (a) Placebo and (b) IVIg.

TABLE 10 Mean (SD) difference between average pain and average baseline pain

	Trial arm	
Variable	Placebo	IVIg
Mean (SD) difference	–0.55 (1.17)	–0.32 (0.74)

SD, standard deviation.

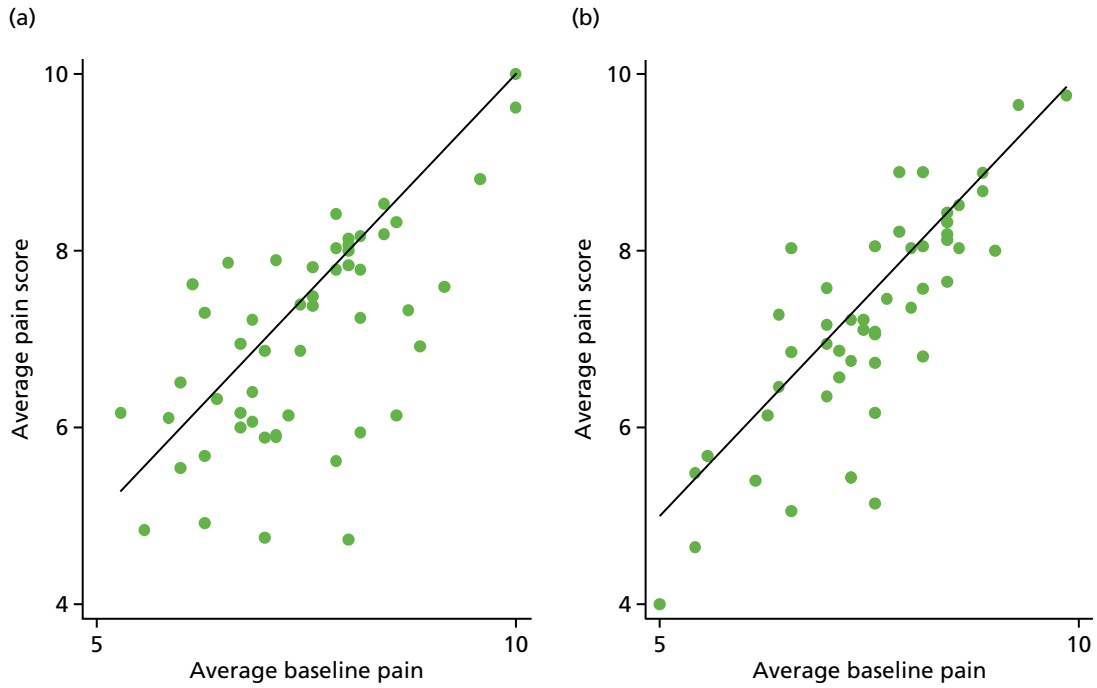

FIGURE 8 Average pain vs. average baseline pain for each participant. (a) Placebo and (b) IVIg.

Sixty-nine (67%) participants had lower pain scores following treatment. This was very similar in both arms [35/53 (66%) for the placebo arm and 34/50 (68%) for the IVIg arm]. Four participants achieved 30% pain reduction: three in the placebo arm and one in the IVIg arm. Only one participant in the placebo arm achieved 50% pain reduction.

Sensitivity analyses

Primary analysis using median pain scores (n = 103)

Median pain scores (over days 6–42) for each participant, by trial arm, are shown in *Figure 9* for the 103 participants included the primary analysis. This plot is similar to that for mean pain, which is unsurprising as the means and medians are highly correlated ($p = 0.97$).

A *t*-test was used to compare these median pain scores across trial arms (with no adjustment for number of values). This produced a treatment effect shown in *Table 11*.

Per-protocol analysis (n = 100)

The per-protocol analysis excludes three participants who received their first infusion between days 4 and 8, although it does include the seven participants who received this infusion on day 0. The IVIg effect is slightly larger but the conclusions are unchanged (*Table 12*).

All participants ($n = 111$)

A further analysis was performed including all randomised participants. However, the five participants that did not produce any outcome pain data are essentially excluded from the model. The IVIg effect is very similar to that from the primary analysis and the conclusions are again unchanged (*Table 13*).

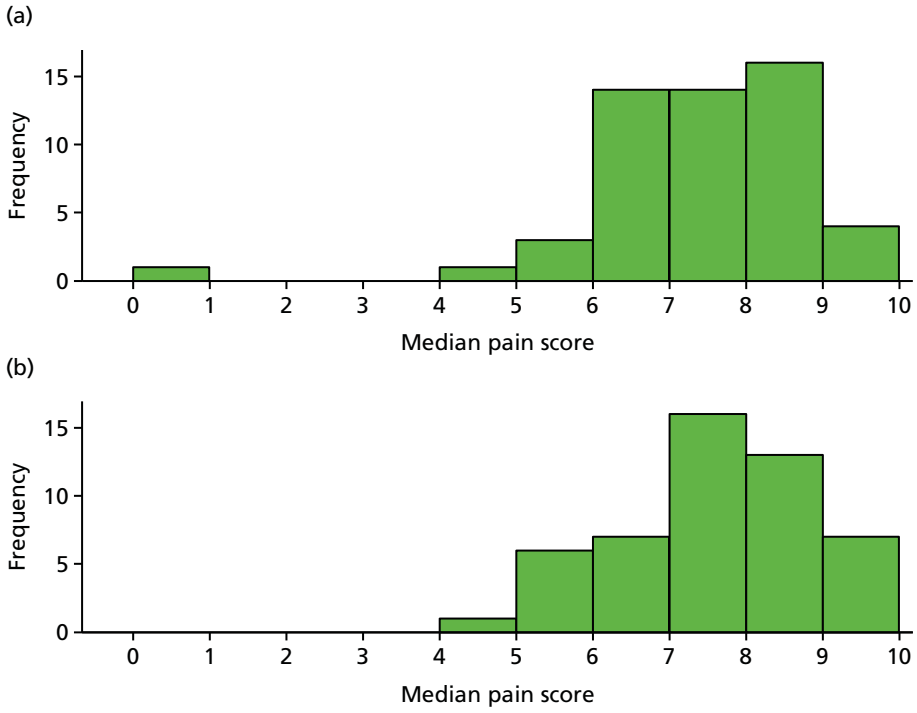

FIGURE 9 Median pain score for each participant by trial arm. (a) Placebo and (b) IVIg.

TABLE 11 Treatment effect from analysis of median pain scores

Variable	Coefficient (95% CI)	*p*-value
Average pain (IVIg – placebo)	0.23 (–0.35 to 0.80)	0.44

TABLE 12 Treatment effect from per-protocol analysis

Variable	Coefficient (95% CI)	*p*-value
Average pain (IVIg – placebo)	0.32 (–0.21 to 0.84)	0.24

TABLE 13 Treatment effect from all randomised participants analysis

Variable	Coefficient (95% CI)	*p*-value
Average pain (IVIg – placebo)	0.23 (–0.28 to 0.75)	0.37

Exploratory analyses

Pain scores over time

The average pain scores for each day, by trial arm, are shown in *Figure 10*. This indicates that there is clear separation between the pain scores in the trial arms on most days, although the difference is relatively small. In addition, it can be seen that average pain score in both groups is fairly constant over time.

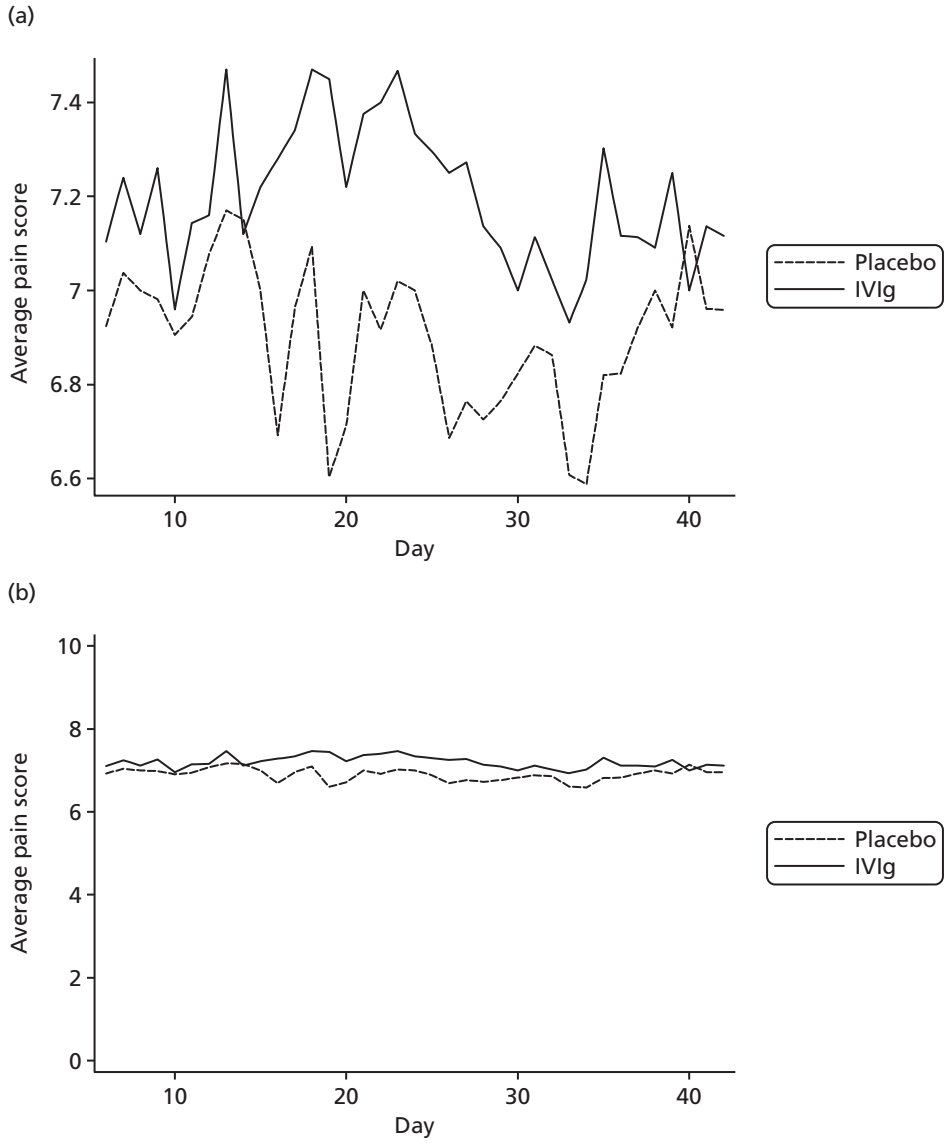

FIGURE 10 Average pain for each day by trial arm (different *y*-axes) with (a) showing truncated pain score at 6.6.

Treatment effect by site (n = 103)

The primary analysis was repeated with a separate treatment effect for each site. The treatment effects for each site are shown in *Table 14*. We note that pain scores are lower for the placebo arm in all centres except Glasgow; however, there is no statistical evidence for a difference in treatment effects ($p = 0.68$), but we note that this study was not powered for such a comparison.

Treatment effect by complex regional pain syndrome type (n = 100)

The primary analysis was repeated with a separate treatment effect for CRPS type I and II. Three participants with 'undecided' CRPS type were omitted from this analysis. The treatment effects for each CRPS type are shown in *Table 15*. We note that pain scores are lower for IVIg for participants with CRPS type II. In addition, there is weak evidence for a difference in treatment effects ($p = 0.02$) between the two CRPS types.

Treatment effect by number of infusions (n = 103)

The primary analysis was repeated with a separate treatment effect for patients who either did or did not receive their second (blind) infusion. The treatment effects for both groups are shown in *Table 16* but there is no statistical evidence for a difference in these effects ($p = 0.29$).

TABLE 14 Treatment effects for each site

Average pain (IVIg – placebo)	Number of participants	Coefficient (95% CI)
Bath	9	0.90 (–0.83 to 2.64)
Cambridge	8	1.10 (–0.73 to 2.93)
Glasgow	17	–0.61 (–1.87 to 0.65)
Leicester	6	0.86 (–1.25 to 2.97)
Liverpool	30	0.03 (–0.92 to 0.98)
London	27	0.41 (–0.58 to 1.41)
Norwich	6	0.75 (–1.36 to 2.87)

TABLE 15 Treatment effects for each CRPS type

Variable	Number of participants	Coefficient (95% CI)
CRPS type I	88	0.44 (–0.11 to 0.98)
CRPS type II	12	–1.51 (–3.00 to –0.03)

TABLE 16 Treatment effects by number of infusions

Number of infusions	Number of participants	Coefficient (95% CI)
1. First only	6	–1.38 (–4.29 to 1.53)
2. Both blind	97	0.32 (–0.21 to 0.86)

This analysis was extended to include whether or not participants received open-phase infusions. Again, there is no statistical evidence for a difference in treatment effects ($p = 0.74$) (*Table 17*).

Treatment effect by disease duration (n = 103)

The primary analysis was repeated with a separate treatment effect for each disease duration (1–5 years). There is little evidence to suggest that treatment effect depends on disease duration ($p = 0.33$).

This analysis was repeated, treating disease duration as a continuous variable (*Table 18*). The interaction term (treatment × duration) was negative (–0.32, 95% CI –0.77 to 0.13), suggesting that treatment might be effective for those of longer disease duration. However, this term was not statistically significant ($p = 0.16$).

TABLE 17 Treatment effects by number of infusions (including open phase)

Number of infusions	Number of participants	Coefficient (95% CI)
1. First blind only	6	–1.38 (–4.25 to 1.49)
2. Both blind	8	0.34 (–1.60 to 2.28)
3. Both blind and first open[a]	15	0.30 (–1.14 to 1.74)
4. All	74	0.29 (–0.31 to 0.90)

a Includes one participant who missed their first open infusion but received their second.

TABLE 18 Treatment effects by disease duration

Disease duration (years)	Number of patients	Coefficient (95% CI)
1	30	0.90 (–0.04 to 1.85)
2	26	0.47 (–0.58 to 1.52)
3	22	–0.56 (–1.66 to 0.54)
4	23	–0.03 (–1.12 to 1.06)
5	2	1.12 (–2.45 to 4.70)

Treatment effect by psychiatric medical history (n = 103)

The primary analysis was repeated with a separate treatment effect for psychiatric medical history (yes/no). There is no evidence for a difference in treatment effects ($p = 0.25$).

Treatment effect by allergy status (n = 103)

The primary analysis was repeated with a separate treatment effect for allergy status (yes/no). There is no evidence for a difference in treatment effects ($p = 0.49$).

Treatment effect by low baseline IgG plasma level (n = 103)

The primary analysis was repeated with a separate treatment effect for low IgG plasma level (< 10/ ≥ 10 mg/dl). There is no evidence for a difference in treatment effects ($p = 0.19$).

Treatment effect adjusted for disease duration (n = 103)

The primary analysis model was refitted after adjusting for disease duration. The treatment effect changed little (0.27, 95% CI –0.26 to 0.79).

The correlation between pain difference (blinded phase – baseline) and disease duration was calculated for both arms. These values were 0.18 (placebo) and –0.12 (IVIg). These relationships can be seen in *Figure 11*.

Open-label results

Withdrawals from study medication (open phase)

Out of the 111 randomised participants, 12 withdrew their consent to use the study medication during the blinded phase. A further 13 participants withdrew their consent to use the study medication during the open phase. All 13 participants received their first open infusion but none received their second. Further details regarding these participants can be found in *Table 19*.

Open-label infusions

Out of the 99 participants who did not withdraw from study medication during the blinded phase, 90 received their first open infusion (*Table 20*). A total of 77 participants received their second open infusion, including one participant who did not receive their first open infusion. This was due to the participant having to travel abroad owing to a family emergency. However, the participant was eager to have the open-label infusions. The chief investigator was consulted and it was agreed that, on compassionate grounds, the participant would be able to attend for the second open-label infusion at the set time point.

Two of the 'ineligible' participants received both infusions; these participants are excluded from the following analyses, which use the 'primary analysis' sample.

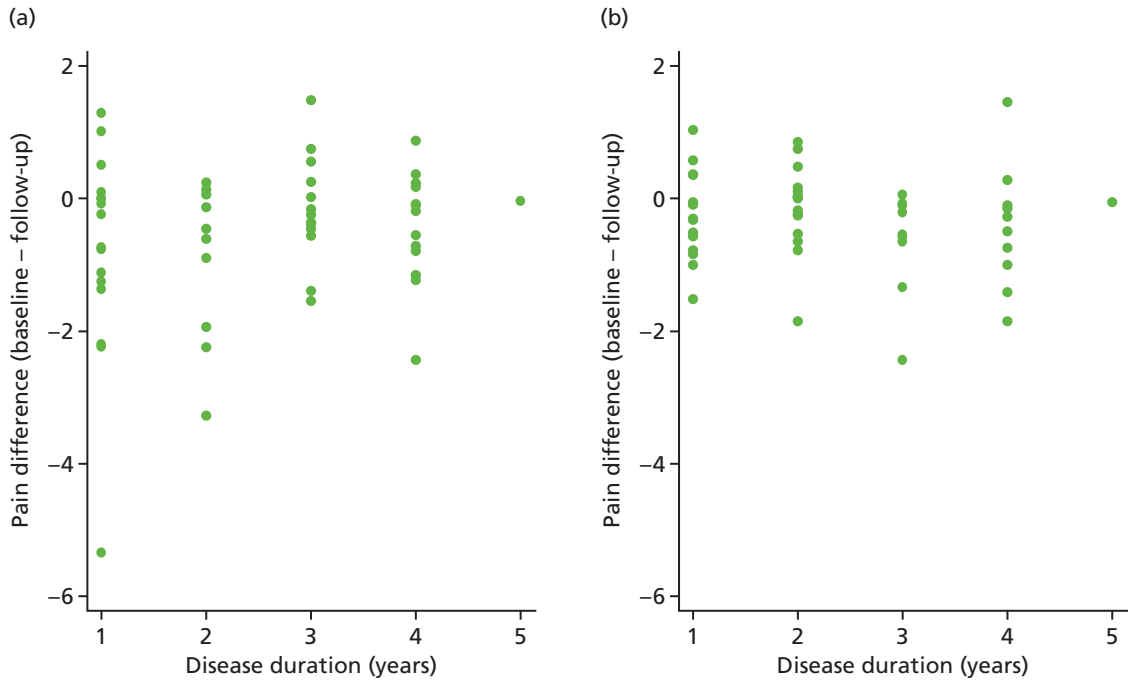

FIGURE 11 Pain difference (baseline – follow-up) vs. disease duration. (a) Placebo and (b) IVIg.

TABLE 19 Details of withdrawals during open phase

Day	Treatment	Reason for withdrawal	Open infusion 1?	Open infusion 2?
44	Placebo	AE (participant withdrew)	Yes	No
50	Placebo	AE (participant withdrew)	Yes	No
51	Placebo	AE (participant withdrew)	Yes	No
59	Placebo	AE (participant withdrew)	Yes	No
62	Placebo	AE (participant withdrew)	Yes	No
62	IVIg	AE (team withdrew)	Yes	No
63	Placebo	AE (participant withdrew)	Yes	No
64	IVIg	AE (participant withdrew)	Yes	No
64	IVIg	AE (participant withdrew)	Yes	No
64	Placebo	AE (participant withdrew)	Yes	No
64	Placebo	AE (team withdrew)	Yes	No
69	Placebo	Other (circumstance change)	Yes	No
71	IVIg	AE (team withdrew)	Yes	No

Shaded rows correspond to participants who supplied no outcome data during open phase.

TABLE 20 Number of participants receiving open infusions

		Trial arm	
		Placebo ($n = 56$)	IVIg ($n = 55$)
Did participant receive first open infusion?	Yes	49 (87.5%)	41 (74.5%)
Did participant receive second open infusion?	Yes	39 (69.6%)	38 (69.1%)

Average pain score by day

Average pain scores for each day, by trial arm, are shown in *Figure 12* based on all available data at each time point for days 1 to 84. Note that the number of participants decreases for the open-label period (*Table 21*).

Reduction in pain score: open versus blinded

The difference between (average) open-label pain score and blinded pain score is plotted in *Figure 13* for each participant. These differences are also summarised in *Table 22*.

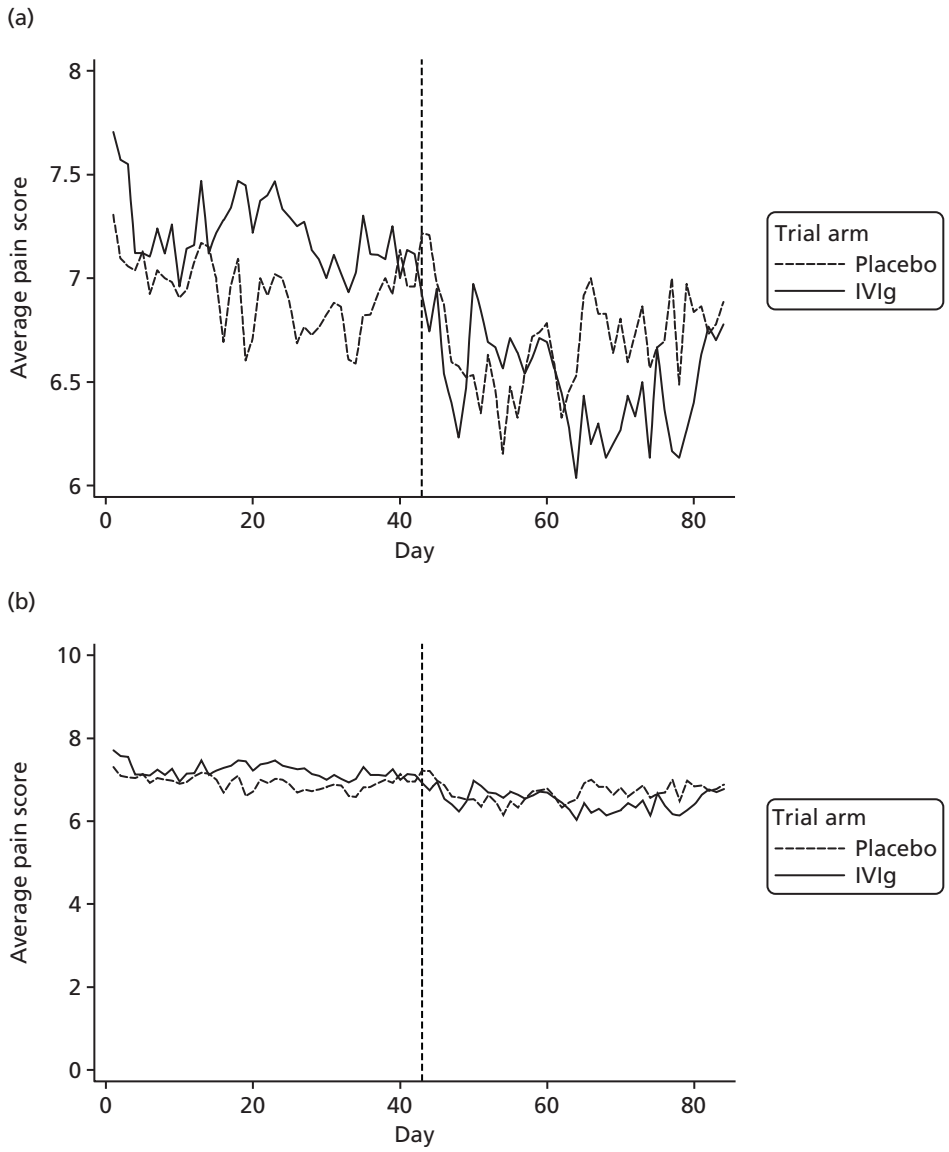

FIGURE 12 Average pain for each day by trial arm (different *y*-axes) with (a) showing truncated at 6.

TABLE 21 Mean/median pain per visit (NRS score)

		Day			
Study group	Baseline	1	22	43	64
Placebo	7.5/8 ($n = 52$)	7.3/7 ($n = 49$)	6.9/7.5 ($n = 48$)	7.2/8 ($n = 46$)	6.5/7 ($n = 34$)
IVIg	7.5/8 ($n = 50$)	7.7/8 ($n = 44$)	7.4/8 ($n = 45$)	6.8/7 ($n = 39$)	6.0/7 ($n = 28$)

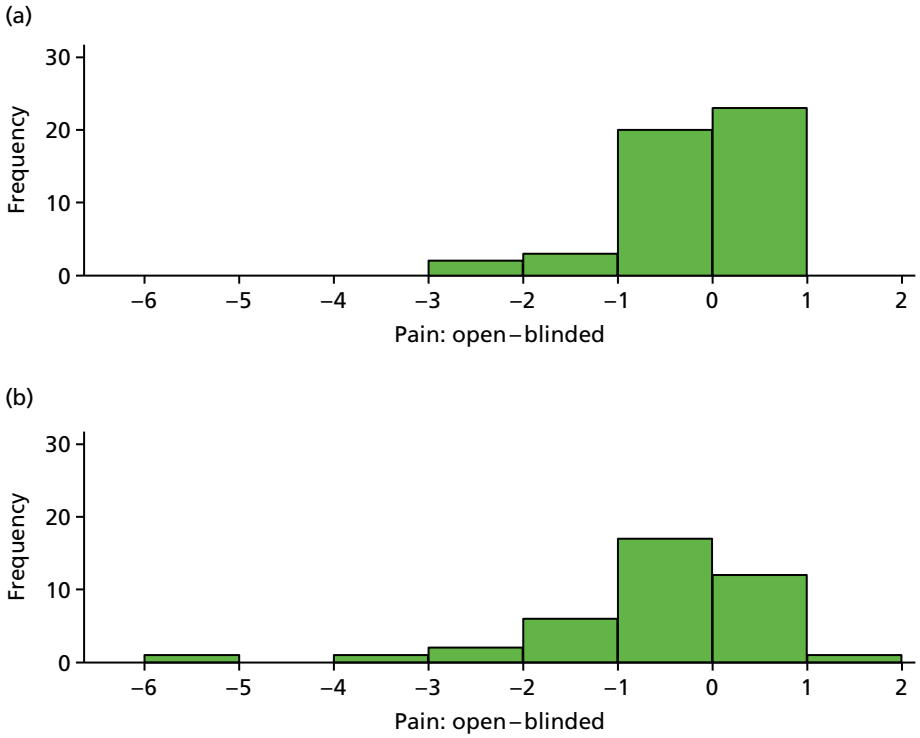

FIGURE 13 Difference between open-label pain and blinded pain for each participant. (a) Placebo and (b) IVIg.

TABLE 22 Mean (SD) difference between open-label and blinded pain (open – blinded)

	Trial arm	
Variable	Placebo ($n = 48$)	IVIg ($n = 40$)
Mean (SD) difference	–0.13 (0.76)	–0.58 (1.25)

SD, standard deviation.

The average open-label pain scores were also plotted against the average blinded phase pain scores for 88 participants (*Figure 14*). Fifty-two (59%) participants had lower pain scores in the open phase [25/48 (52%) for the placebo arm and 27/40 (68%) for the IVIg arm].

Reduction in baseline pain score: open versus baseline

The difference between average baseline pain score and average open-label pain score is plotted in *Figure 15* for each participant. These differences are also summarised in *Table 23*.

Average pain scores from the open phase were plotted against average baseline pain scores for 88 participants (*Figure 16*). Sixty-two (70%) participants had lower pain scores in the open phase [33/48 (69%) for the placebo arm and 29/40 (73%) for the IVIg arm].

Comparison of pain relief: blind and open

Table 24 shows the number of participants achieving 'considerable' pain relief compared with that at baseline. This is based on the 88 participants who provided both blinded and open-phase pain scores.

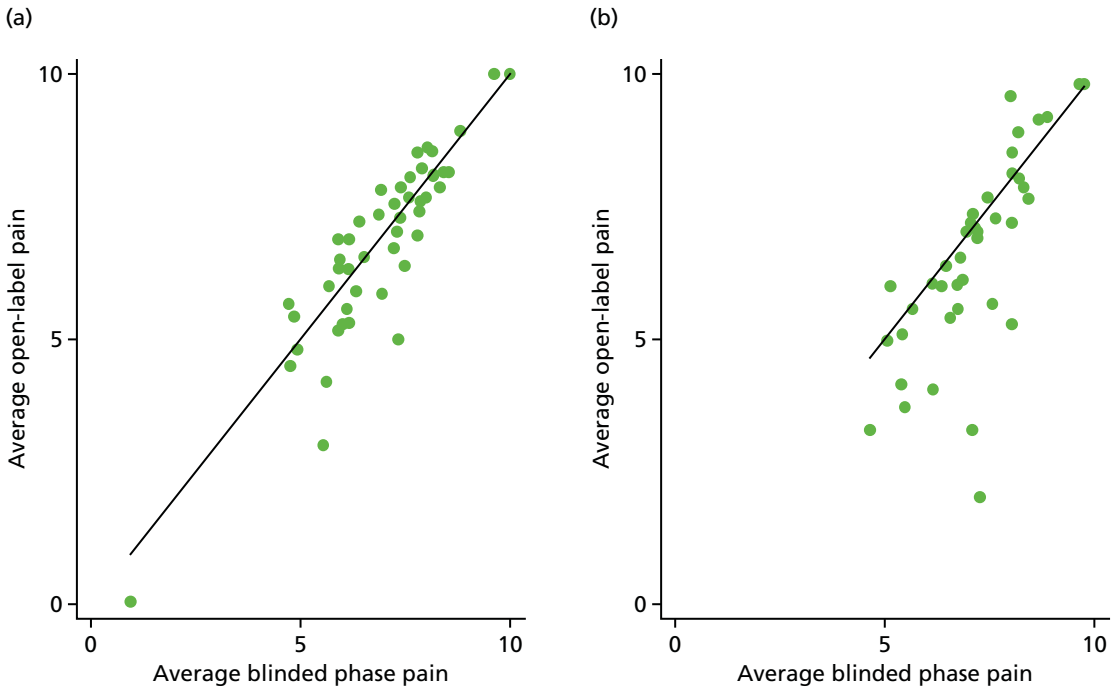

FIGURE 14 Average open-label pain vs. average blinded phase pain for each participant. (a) Placebo and (b) IVIg.

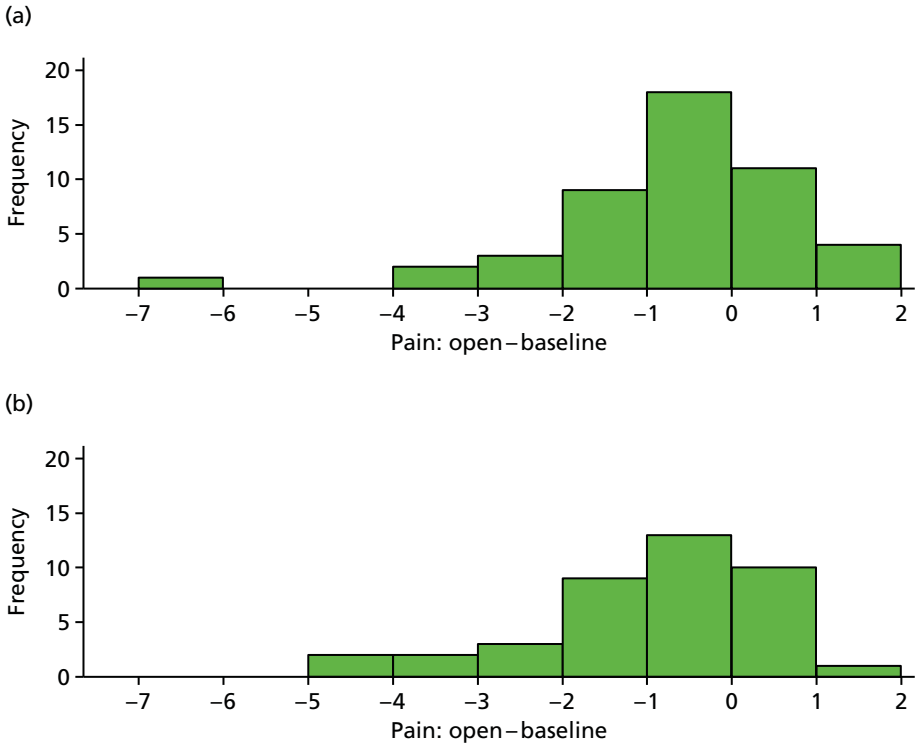

FIGURE 15 Difference between open-label pain and baseline pain for each participant. (a) Placebo and (b) IVIg.

TABLE 23 Mean (SD) difference between open-label and baseline pain

Variable	Trial arm	
	Placebo ($n = 48$)	IVIg ($n = 40$)
Mean (SD) difference	–0.67 (1.46)	–0.92 (1.37)

SD, standard deviation.

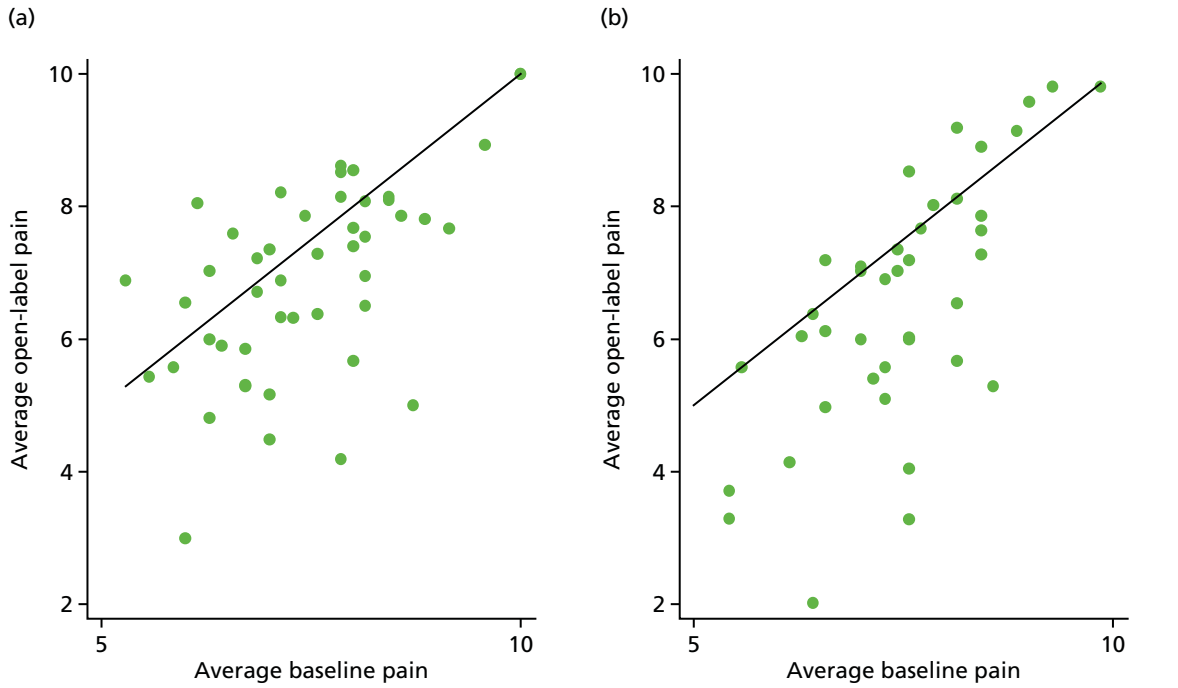

FIGURE 16 Average open-label pain vs. average baseline pain for each participant. (a) Placebo and (b) IVIg.

TABLE 24 Participants achieving pain relief (vs. baseline)

Pain relief	Trial arm			
	Placebo ($n = 48$)		IVIg ($n = 40$)	
	Blinded	Open	Blinded	Open
≥ 2 points	5	6	1	8
30–39%	1	1	1	6
40–49%	1	2	0	1
50–69%	0	1	0	2
≥ 70%	1	1	0	0

Fourteen participants achieved ≥ 2 points' pain relief in the open-label phase and they are described in *Table 25*.

Open-label pain relief by disease duration (n = 88)

The correlation between the difference of (average) follow-up and baseline pain was calculated for both arms. These values were 0.13 (placebo) and –0.33 (IVIg). These relationships can be seen in *Figure 17*.

TABLE 25 Characteristics of participants achieving ≥ 2 points' pain relief in the open phase

IVIg	Pain reduction	Sex	Duration (years)	IgG	Disorder of the immune system and allergies
Placebo	2.33	Male	2	9.7	Yes
Placebo	2.51	Female	2	8.8	No
Placebo	3	Female	3	10.4	No
Placebo	3.67	Female	1	10.4	Yes
Placebo	3.71	Male	3	13	No
Placebo	6.24	Female	1	9.36	Yes
IVIg	2	Female	4	10.4	No
IVIg	2.14	Male	2	11.8	No
IVIg	2.19	Female	4	9.8	No
IVIg	2.48	Male	3	10.07	No
IVIg	3.29	Male	3	13.1	No
IVIg	3.52	Female	4	8.8	Yes
IVIg	4.29	Male	4	10.3	No
IVIg	4.40	Male	2	6.2	No

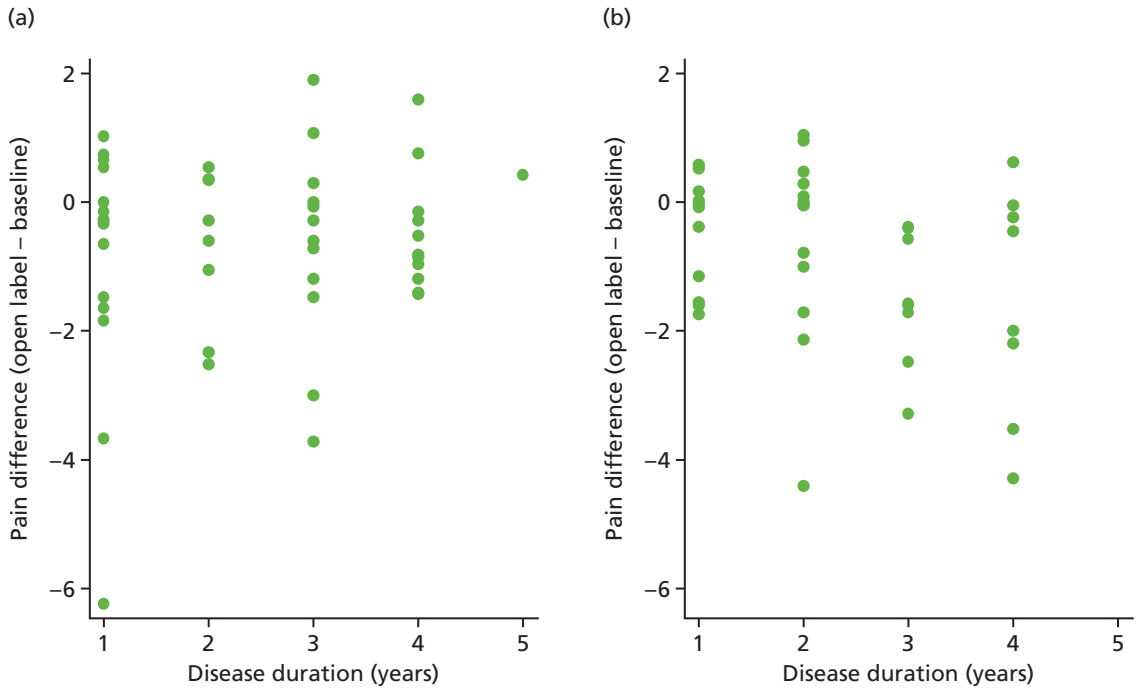

FIGURE 17 Pain difference (open label – baseline) vs. disease duration. (a) Placebo and (b) IVIg.

Secondary outcomes

The analyses of EQ-5D-5L and BPI are adjusted for site. The differences (and CIs) and *p*-values for visit 4 (v4) values are obtained from these adjusted analyses. The differences and CIs for visit 1 (v1) and visit 3 (v3) values are unadjusted. All analyses are based on the primary analysis data set ($n = 103$), that is, they relate to the blinded phase.

EuroQol-5 Dimensions, five-level version

There is little difference in EQ-5D between trial arms (*Table 26* and *Figures 18–20*).

Brief Pain Inventory

There is no evidence of a difference in BPI between the trial arms (*Table 27* and *Figures 21* and *22*).

All differences (and CIs) and *p*-values for the exploratory outcomes are unadjusted. All analyses are based on the primary analysis data set ($n = 103$).

The odds ratio (from ordinal regression) is 1.22 (95% CI 0.57 to 2.59; $p = 0.61$).

TABLE 26 Differences in EQ-5D-5L between trial arms

	Trial arm					
	Placebo		IVIg		IVIg – placebo	
Variable	*n*	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)	*p*-value
v1. EQ-5D-5L	53	0.34 (0.28)	50	0.33 (0.26)	–0.01 (–0.12 to 0.09)	
v3. EQ-5D-5L	53	0.37 (0.29)	45	0.35 (0.25)	–0.02 (–0.13 to 0.09)	
v4. EQ-5D-5L[a]	51	0.37 (0.29)	43	0.41 (0.27)	0.03 (–0.08 to 0.15)	0.58

SD, standard deviation.
a CI/test adjusted for site.

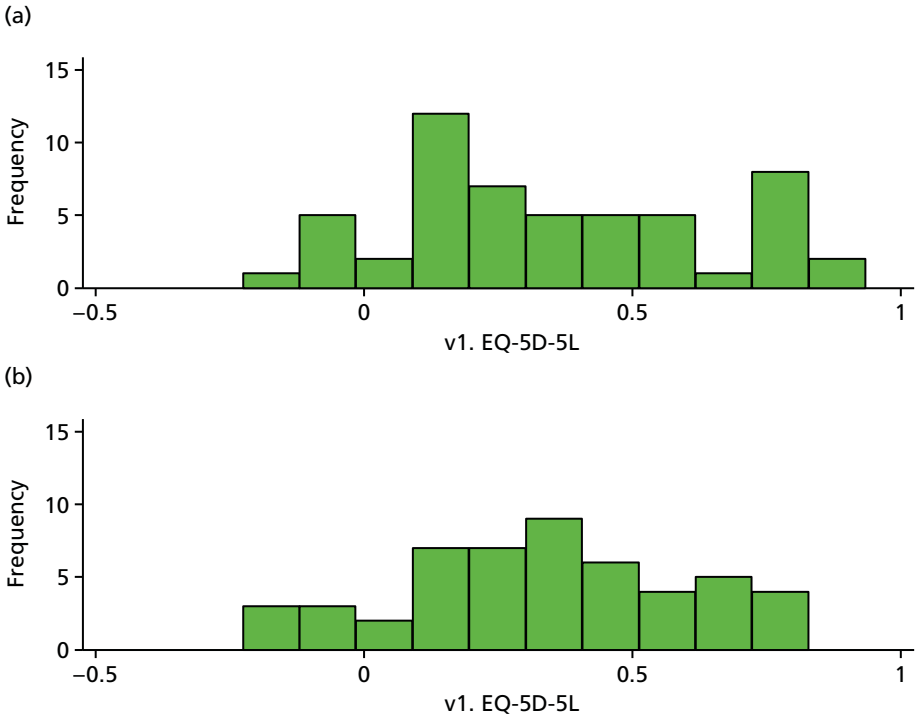

FIGURE 18 Baseline EQ-5D. (a) Placebo and (b) IVIg.

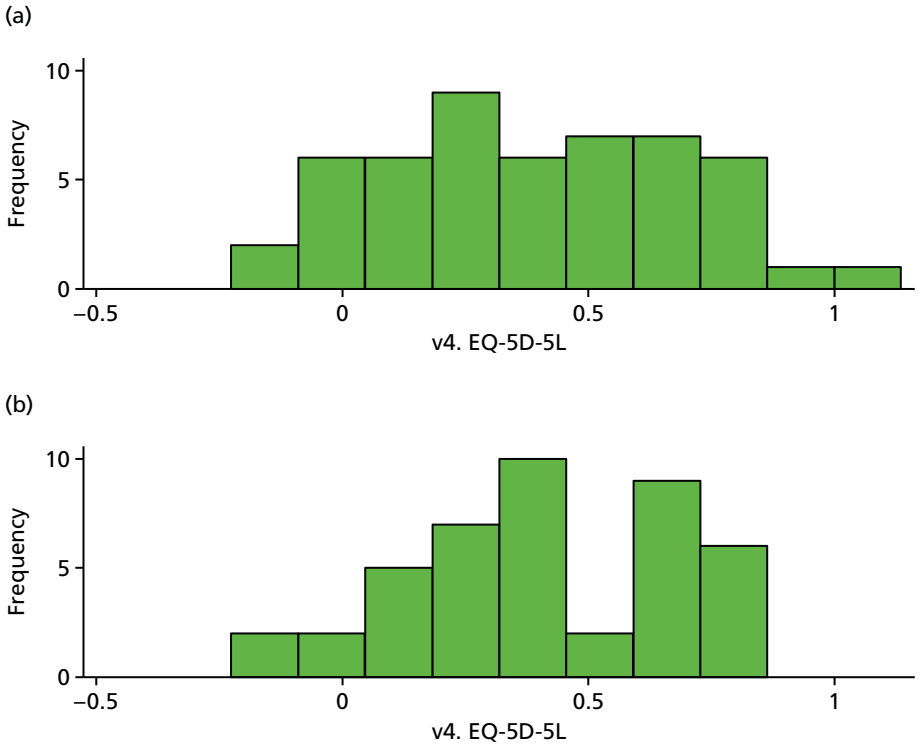

FIGURE 19 EQ-5D (visit 4). (a) Placebo and (b) IVIg.

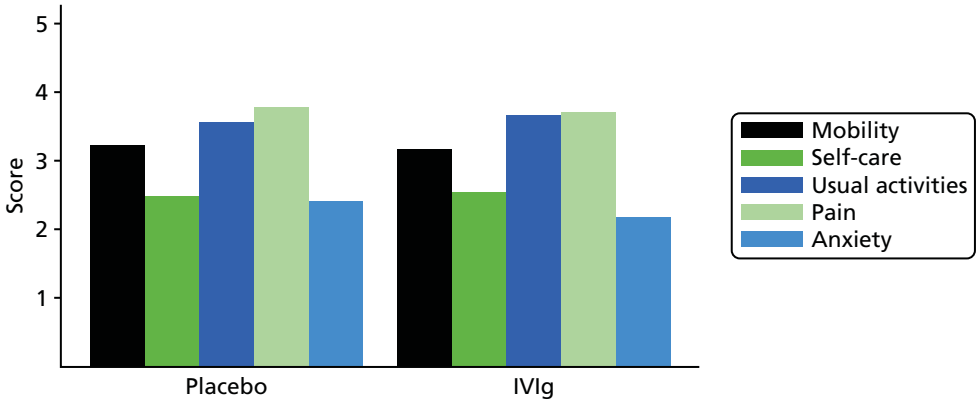

FIGURE 20 EQ-5D domains (visit 4).

TABLE 27 Differences in BPI between trial arms

	Trial arm					
	Placebo		IVIg		IVIg – placebo	
Variable	*n*	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)	*p*-value
v1. BPI interference	53	7.31 (1.63)	50	7.43 (1.64)	0.12 (–0.52 to 0.76)	
v3. BPI interference	53	6.98 (1.94)	45	7.34 (1.30)	0.36 (–0.32 to 1.03)	
v4. BPI interference[a]	51	6.89 (2.08)	44	7.24 (1.54)	0.35 (–0.43 to 1.13)	0.38

SD, standard deviation.
a CI/test adjusted for site.

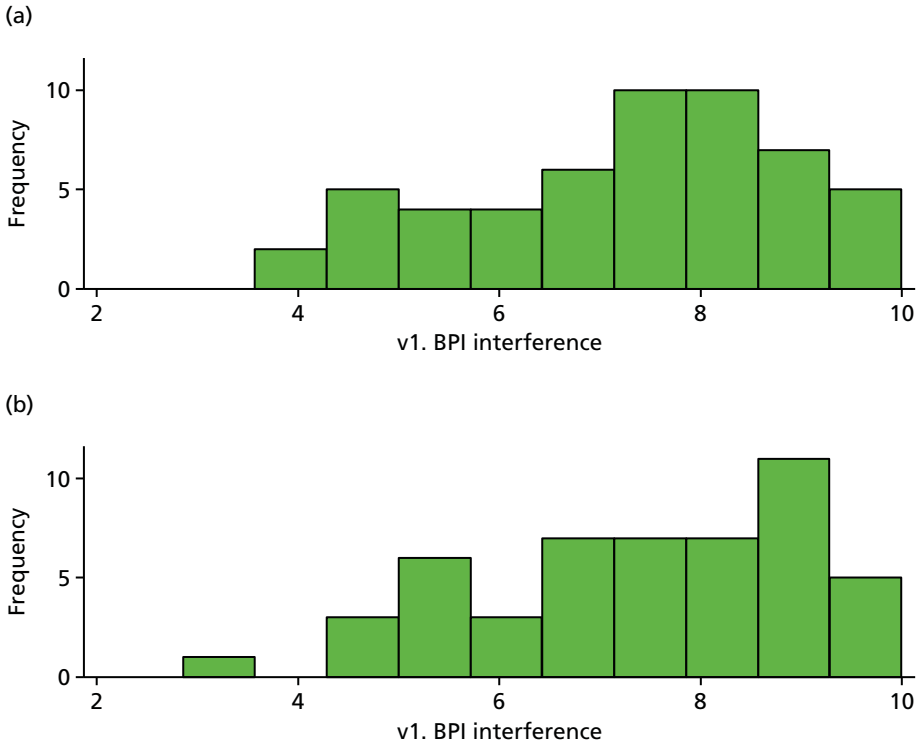

FIGURE 21 Baseline BPI. (a) Placebo and (b) IVIg.

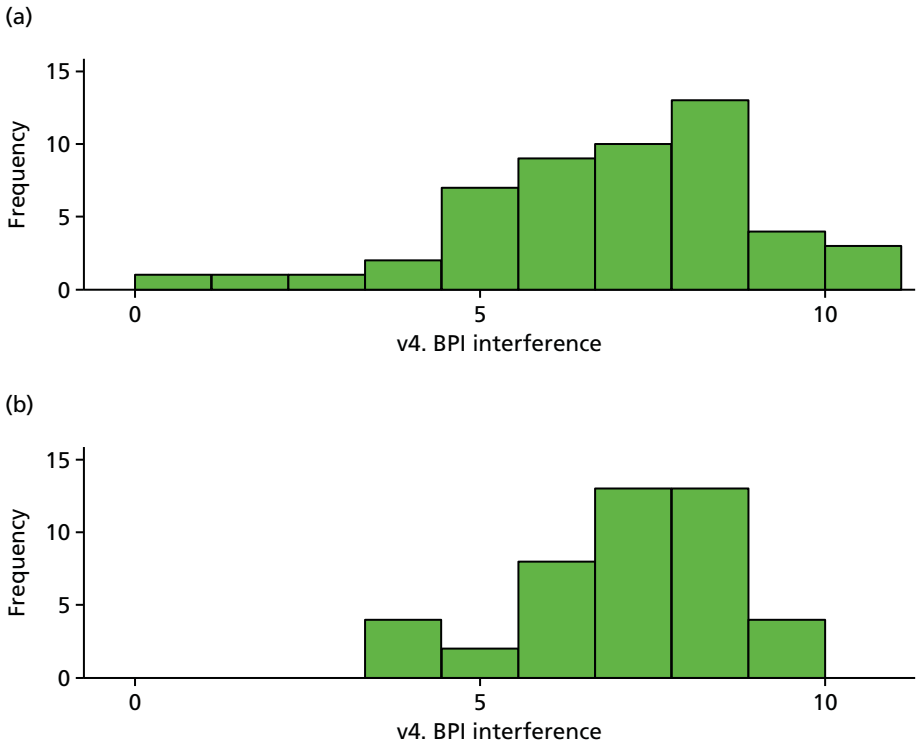

FIGURE 22 The BPI (visit 4). (a) Placebo and (b) IVIg.

Limb temperature and volume

Limb volume was very skewed and, hence, a cube root transformation was applied before analysis. There is weak evidence of a difference in affected limb volumes at visit 4 (*Tables 28* and *29* and *Figure 23*).

*Other questionnaires (*Tables 30–35 *and* Figure 24*)*

A total of six SAEs were reported overall by six patients across the blinded and open-label phases of the trial. There were no suspected unexpected serious adverse reactions reported (*Tables 36–39*).

TABLE 28 Limb volume and temperature

	Trial arm					
	Placebo		IVIg			
Variable	*n*	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)	*p*-value
Cube root volume						
v1. Non-affected limb	43	9.32 (1.93)	40	9.50 (2.44)	0.18 (–0.78 to 1.14)	
v1. Affected limb	43	9.34 (1.94)	40	9.52 (2.49)	0.18 (–0.79 to 1.15)	
v4. Non-affected limb	40	8.96 (2.17)	35	9.30 (2.48)	0.34 (–0.73 to 1.41)	0.525
v4. Affected limb	40	8.70 (2.05)	35	9.72 (2.60)	1.02 (–0.05 to 2.09)	0.061
Temperature						
v1. Non-affected limb	44	29.55 (2.61)	44	29.87 (2.69)	0.32 (–0.80 to 1.45)	
v1. Affected limb	44	28.88 (3.44)	44	28.96 (3.33)	0.09 (–1.35 to 1.52)	
v4. Non-affected limb	42	29.29 (2.33)	36	29.06 (2.31)	–0.23 (–1.28 to 0.82)	0.661
v4. Affected limb	42	28.68 (3.02)	36	27.92 (2.63)	–0.75 (–2.04 to 0.53)	0.247

SD, standard deviation.

TABLE 29 Participant weight

	Trial arm					
	Placebo		IVIg			
Variable	*n*	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)	*p*-value
v2. Participant weight (kg)	53	81.77 (20.96)	50	84.47 (19.64)	2.71 (–5.25 to 10.66)	0.501
v3. Participant weight (kg)	52	82.13 (20.96)	45	85.32 (20.07)	3.18 (–5.13 to 11.49)	0.449
v4. Participant weight (kg)	49	81.67 (20.64)	39	85.11 (20.51)	3.44 (–5.34 to 12.22)	0.438

SD, standard deviation.
Participant weight was recorded at visits 2, 3 and 4.

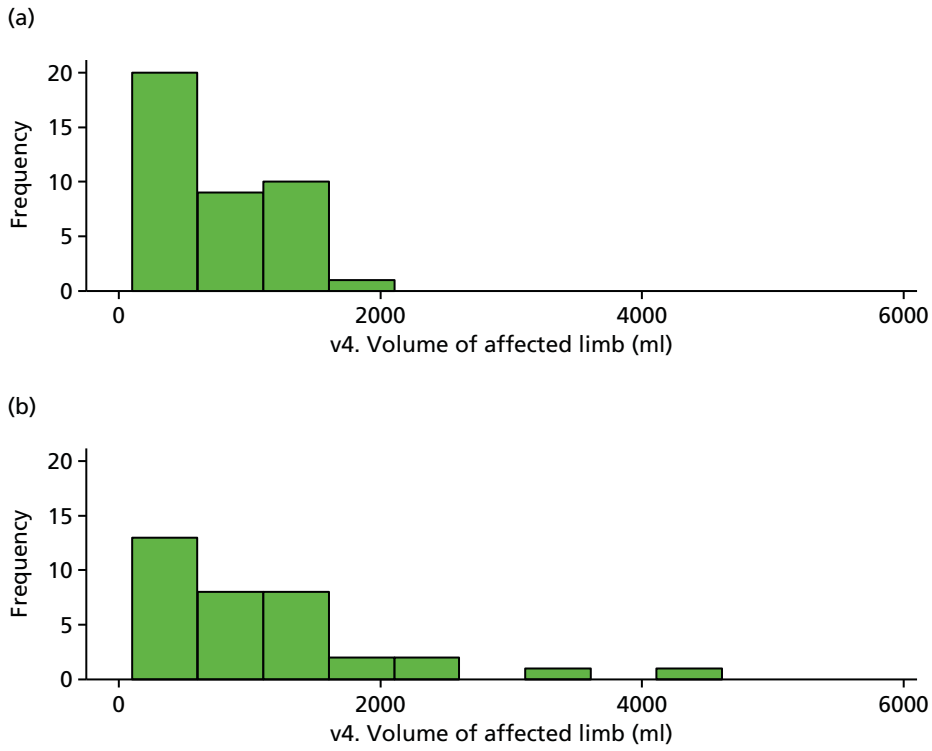

FIGURE 23 Volume of affected limb (visit 4). (a) Placebo and (b) IVIg.

TABLE 30 McGill (short form)

	Trial arm					
	Placebo		IVIg			
Variable	*n*	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)	*p*-value
McGill: continuous pain						
v1. McGill: continuous pain	52	6.20 (1.67)	50	6.09 (1.80)	–0.11 (–0.79 to 0.57)	
v3. McGill: continuous pain	51	5.57 (2.06)	45	5.99 (1.93)	0.42 (–0.40 to 1.23)	
v4. McGill: continuous pain	50	5.36 (2.24)	44	5.23 (2.46)	–0.12 (–1.09 to 0.84)	0.802
McGill: intermittent pain						
v1. McGill: intermittent pain	52	5.68 (2.34)	50	5.94 (2.09)	0.26 (–0.61 to 1.14)	
v3. McGill: intermittent pain	52	5.00 (2.49)	45	5.44 (2.42)	0.45 (–0.54 to 1.44)	
v4. McGill: intermittent pain	50	4.93 (2.65)	44	4.86 (2.44)	–0.07 (–1.12 to 0.98)	0.894
McGill: neuropathic pain						
v1. McGill: neuropathic pain	53	5.80 (2.17)	50	6.04 (1.69)	0.24 (–0.53 to 1.00)	
v3. McGill: neuropathic pain	53	5.18 (2.13)	45	5.47 (1.77)	0.29 (–0.50 to 1.08)	
v4. McGill: neuropathic pain	51	4.92 (2.41)	44	5.10 (2.06)	0.18 (–0.74 to 1.10)	0.697

continued

TABLE 30 McGill (short form) (*continued*)

Variable	Trial arm: Placebo *n*	Placebo Mean (SD)	IVIg *n*	IVIg Mean (SD)	Difference (95% CI)	*p*-value
McGill: affective						
v1. McGill: affective	52	5.16 (2.17)	50	5.21 (2.33)	0.05 (–0.83 to 0.94)	
v3. McGill: affective	51	4.72 (2.54)	45	5.44 (2.28)	0.73 (–0.25 to 1.71)	
v4. McGill: affective	50	4.52 (2.65)	44	4.89 (2.45)	0.37 (–0.68 to 1.42)	0.484
McGill: total score						
v1. McGill: total score	52	5.74 (1.63)	50	5.88 (1.54)	0.14 (–0.49 to 0.76)	
v3. McGill: total score	51	5.14 (1.93)	45	5.60 (1.74)	0.46 (–0.29 to 1.21)	
v4. McGill: total score	50	4.96 (2.22)	44	5.03 (2.03)	0.07 (–0.80 to 0.95)	0.872

SD, standard deviation.

TABLE 31 HADS

Variable	Trial arm: Placebo *n*	Placebo Mean (SD)	IVIg *n*	IVIg Mean (SD)	Difference (95% CI)	*p*-value
HADS anxiety						
v1. HADS anxiety	53	10.68 (4.59)	50	10.38 (4.77)	–0.30 (–2.13 to 1.53)	
v3. HADS anxiety	53	9.64 (4.75)	45	9.93 (4.71)	0.29 (–1.61 to 2.20)	
v4. HADS anxiety	51	9.78 (4.88)	44	9.41 (4.57)	–0.37 (–2.30 to 1.57)	0.706
HADS depression						
v1. HADS depression	53	10.98 (4.19)	50	9.40 (3.55)	–1.58 (–3.11 to –0.06)	
v3. HADS depression	53	10.43 (4.39)	45	10.36 (3.84)	–0.08 (–1.75 to 1.59)	
v4. HADS depression	51	9.94 (4.47)	44	9.91 (3.65)	–0.03 (–1.71 to 1.65)	0.973

HADS, Hospital Anxiety and Depression Scale; SD, standard deviation.

TABLE 32 Pain catastrophising scale

	Trial arm					
	Placebo		IVIg			
Variable	*n*	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)	*p*-value
PCS rumination						
v1. PCS rumination	53	9.42 (4.38)	50	9.24 (4.27)	–0.18 (–1.87 to 1.52)	
v3. PCS rumination	53	8.77 (4.87)	45	9.84 (4.24)	1.07 (–0.78 to 2.92)	
v4. PCS rumination	51	8.29 (5.25)	44	8.18 (4.62)	–0.11 (–2.14 to 1.92)	0.913
PCS magnification						
v1. PCS magnification	53	4.32 (3.24)	50	3.84 (3.11)	–0.48 (–1.72 to 0.76)	
v3. PCS magnification	53	3.51 (2.94)	45	3.67 (2.77)	0.16 (–1.00 to 1.31)	
v4. PCS magnification	51	3.84 (3.06)	44	3.66 (2.87)	–0.18 (–1.40 to 1.03)	0.764
PCS helplessness						
v1. PCS helplessness	53	11.94 (5.61)	50	12.42 (5.98)	0.48 (–1.79 to 2.74)	
v3. PCS helplessness	53	11.08 (6.25)	45	11.58 (6.11)	0.50 (–1.99 to 2.99)	
v4. PCS helplessness	51	10.53 (6.22)	44	10.18 (5.92)	–0.35 (–2.83 to 2.14)	0.782
PCS total score						
v1. PCS total score	53	25.68 (12.19)	50	25.50 (12.41)	–0.18 (–4.99 to 4.63)	
v3. PCS total score	53	23.36 (13.25)	45	25.09 (11.76)	1.73 (–3.33 to 6.80)	
v4. PCS total score	51	22.67 (13.96)	44	22.02 (12.49)	–0.64 (–6.08 to 4.79)	0.814

PCS, Physical Component Score; SD, standard deviation.

TABLE 33 Participant global impression of change

	Trial arm	
Visit 4	Placebo	IVIg
Very much improved	2	0
Much improved	4	4
Minimally improved	13	13
No change	27	19
Minimally worse	4	6
Much worse	1	1
Very much worse	0	1
Total	51	44

TABLE 34 Stanford Presenteeism Scale

	Trial arm					
	Placebo		IVIg			
Variable	*n*	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)	*p*-value
v1. SPS total score	19	19.63 (3.35)	16	19.44 (3.14)	–0.19 (–2.44 to 2.06)	
v4. SPS total score	19	20.00 (3.35)	12	19.83 (2.86)	–0.17 (–2.56 to 2.22)	0.888

SD, standard deviation.

TABLE 35 Neglect-like symptoms

	Trial arm					
	Placebo		IVIg			
Variable	*n*	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)	*p*-value
v1. NLS mean score	50	4.04 (1.37)	49	3.92 (1.40)	–0.12 (–0.67 to 0.43)	
v4. NLS mean score	47	3.57 (1.37)	41	3.61 (1.10)	0.05 (–0.48 to 0.58)	0.856

SD, standard deviation.

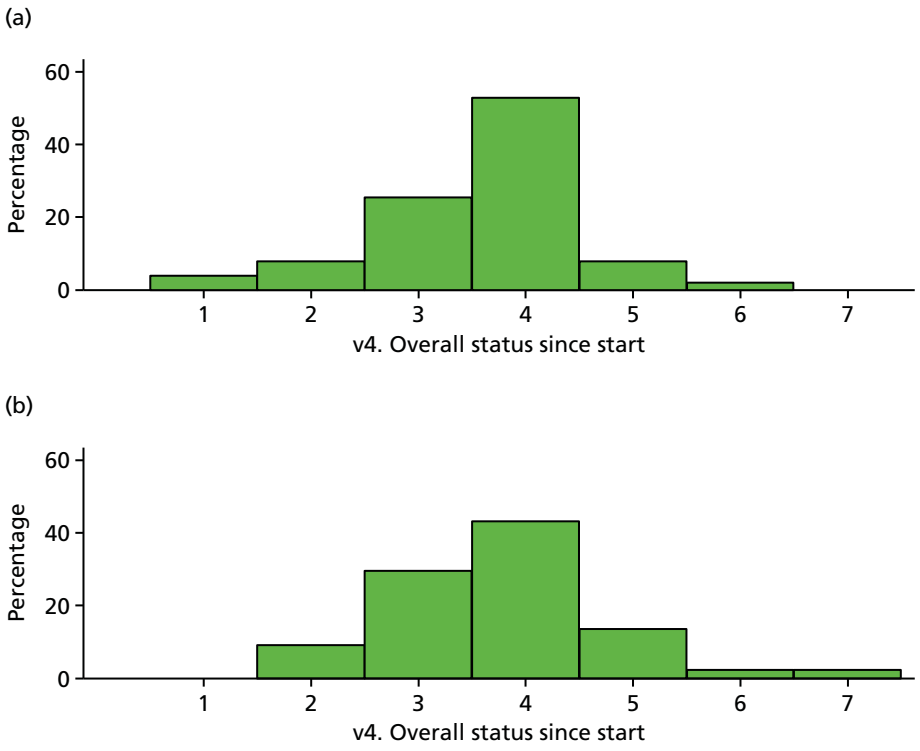

FIGURE 24 Participant global impression of change (visit 4). (a) Placebo and (b) IVIg.

TABLE 36 Expectation from IVIg (visit 2)

	Trial arm				
	Placebo		IVIg		
Variable	*n*	Mean (SD)	*n*	Mean (SD)	Difference (95% CI)
v2. Expected pain level	53	5.25 (2.38)	50	5.52 (1.68)	0.27 (–0.53 to 1.08)

SD, standard deviation.

TABLE 37 Health and social care utilisation (visit 1)

	Trial arm			
	Placebo		IVIg	
Variable	*N*	*n* (%)	*N*	*n* (%)
v1. Contacted GP or health care professional	53	41 (77.4)	50	32 (64.0)
v1. Admitted as inpatient during last 6 weeks	53	2 (3.8)	49	2 (4.1)
v1. Referred as outpatient during last 6 weeks	53	18 (34.0)	50	11 (22.0)
v1. Made contact with other facility during last 6 weeks	53	8 (15.1)	48	7 (14.6)
v1. Prescribed medication during last 6 weeks	53	13 (24.5)	49	8 (16.3)
v1. Contact with social service during last 6 weeks	53	2 (3.8)	50	2 (4.0)

GP, general practitioner.

TABLE 38 The SAEs during the blinded phase

SAE number	TRT	SAE	Code	Intensity	Related	Resolved
1	Placebo	Headache	10. Neurological	Severe	Probably	Yes
		Vomiting	4. Gastro Intestinal	Moderate	Probably	Yes
2	IVIg	Headache	10. Neurological	Severe	Probably	Yes

TRT, treatment group.

TABLE 39 The AEs during the open phase

SAE number	SAE	Code	Intensity	Related	Resolved
3	Aseptic meningitis	10. Neurological	Moderate	Probably	Yes
	Associated symptoms documented				
	Headache	10. Neurological	Moderate	Probably	Yes
	Photopia	10. Neurological	Moderate	Probably	Yes
4	Increased heart rate	10. Neurological	Moderate	Probably	Yes
5	Aseptic meningitis	10. Neurological	Severe	Probably	Yes
6	Deep-vein thrombosis	7. Neurological	Severe	Probably	Yes

Chapter 5 Discussion

In our Phase III RCT, treatment with two low doses of IVIg (0.5 g/kg/treatment) did not change patients' pain. No patient treated with IVIg reported substantial pain reduction, which contrasted with results in earlier studies.[7,9] In addition, the overall placebo response was small.

Trial participants had characteristics typical of patients with long-standing CRPS cared for in a secondary or tertiary setting, including an average age of mid-40s, female-to-male ratio of 2–3 : 1, high pain intensity, high pain interference,[29] low QoL[5] and cold limbs.[30]

The lack of effect on the primary outcome (pain intensity) was underpinned by the finding of no significant effects on mood, pain impact, QoL and limb temperature.

None of the predefined prognostic markers predicted a beneficial treatment response in this trial. The unexpected, post hoc finding of significant pain reduction in the rare group of patients with CRPS II may be due to random effects and would need prospective confirmation.

Potential reasons for the discrepancy between the results in this and prior trials include selection bias and random effects. Although this trial included patients with longer disease durations than the earlier RCT,[9] we found no correlation between disease duration and treatment outcome.

The present standard of care for patients with long-standing CRPS includes physical rehabilitation, psychological support and treatment with drugs and devices, but many patients still experience a high level of pain while on treatment.[31] The findings of this study add to earlier negative trials of immune-modulating treatments, including lenalidomide, intrathecal steroids, infliximab and oral steroids.[32–35] These negative findings should be considered on the background of recent in vivo and in vitro results on functionally active, non-inflammatory autoantibodies in CRPs.[36–38] The target of effective immune-modulating therapy may be the production of such autoantibodies, rather than inflammatory processes.[39] Alternative immune-modulating technologies, such as plasma exchange therapy, disease modifying antirheumatic drugs, high-dose immunoglobulin or B-cell ablation therapies, should be explored; initial results have been encouraging, but RCTs are needed.[40–42] This remains an area of large unmet need, a fact that is also underpinned by the recently discussed, patient-driven, generally futile approaches to achieve pain relief by surgical removal of the painful limb.[43]

The trial strengths include the multicentre set-up, the size, the swift recruitment to plan, the high patient retention (low withdrawal) and the high patient adherence. Patient demographics and disease characteristics are typical for those with long-standing CRPS, as seen in secondary and tertiary care.[29] As patients engaged well, they provided comprehensive data aiding the data quality and statistical analysis. A much higher attrition had been anticipated (see *Chapter 3*) from experience in academic trials of this size. A comprehensive patient recruitment and retention strategy was essential to this achievement; details will be published separately. Blinding was tested and was successful.

The study is limited by the upper disease duration of 5 years and the lower cut-off point of 1 year, the short dosing, and the lack of a high-dose treatment arm. Although the study was well balanced overall, there was some imbalance in the health resource use, with a higher use in the placebo arm. The trial was not powered for the individual subgroup evaluations.

Chapter 6 Conclusion

In conclusion, contrary to our expectation, low-dose immunoglobulin treatment did not produce pain relief in patients with long-standing moderate and severe CRPS of up to 5 years duration. Additional research might include the assessment of treatment effects in patients with severe concomitant autoimmunity or in patients with CRPS type II. Because recent laboratory findings have suggested that there might be an autoantibody contribution in many CRPS, alternative immune modulating treatment or higher-dose IVIg treatment should be further examined.

Using comprehensive recruitment strategies, the completion of this trial for a rare condition within 2 years as per the plan in a UK setting is encouraging, and should reassure investigators wishing to perform clinical trials in this and other rare chronic pain conditions that this is possible in a feasible time frame.

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Trial Steering Committee

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Data sharing statement

All available data can be obtained by contacting the corresponding author.

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Appendix 1 Patient information sheet

Low-dose **I**ntravenous Immunoglobulin Treatment for Complex Regional **P**ain **S**yndrome

The LIPS Trial

Patient Information Sheet
(date: 02.09.2013; version 3.0)

Dear patient,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Chief investigator:

Dr. Andreas Goebel, Consultant in Pain Medicine, University of Liverpool

Principal investigator:

What is the purpose of the study?

Complex Regional Pain Syndrome (CRPS) is often a distressing condition, which in many cases is difficult to treat.

Intravenous immunoglobulin (IVIG) is a drug, which has been used for over 30 years to effectively treat other health conditions, but has only recently been researched as a treatment for pain such as yours. We think that IVIG may be effective in CRPS because IVIG affects the immune system and we know that the immune system is involved in pain such as yours.

In this study our aim is to find out if intravenous immunoglobulin can relieve chronic pain better than a dummy drug.

The duration of the main study is 12 weeks, and involves four visits. The main study is followed by an optional 'open label' study, which lasts a further 12 weeks and involves one more visit.

What is the drug or procedure that is being tested?

Immunoglobulin is purified from plasma from the blood of more than 1000 donors. Plasma is the fluid portion of the blood from which the cells have been removed. It contains 'immunoglobulin molecules' that are substances which normally fight infections and control inflammation but can sometimes cause disease. Immunoglobulin is used to treat other conditions where the immune system is thought to be causing disease. It is given by infusion through a small plastic needle inserted into a vein usually in the forearm (intravenous infusion).

Why have I been chosen?

- Because you suffer from a particular type of pain, which is called "Complex Regional Pain Syndrome (CRPS)", and
- Because you feel that your pain medication and physiotherapy do not reduce your pain enough.
- We wish to study a total of 108 patients with pain such as yours in research centres across the UK.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. 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 standard of care you receive.

What will happen to me if I take part?

You will be given intravenous infusions on day 1 and day 22. The infusions will either be the true treatment (immunoglobulin), or dummy treatment, which looks the same but is actually a harmless inactive substance (placebo).
You may have further infusions of true treatment on day 43 and day 64, if you wish. You can participate in the trial without having these further infusions on day 43 and 64, if you do not want them. All infusions are given in hospital and take about five hours. You will need to keep pain diaries and answer questionnaires as in the next section.

.
What do I have to do?

- We need you to complete pain diaries and questionnaires at the times described in the study-plan attached.
- We will also need to interview you at the agreed times. You will have to come to the clinic at least four times (for the durations of each visit see study-plan)- and up to five times in total should you decide to receive the optional infusions on days 43 and 64, see below.
- We will also ask you to give blood on two separate occasions: Before you receive your first infusion (40 ml in total, which is about 8 teaspoons. Of this 30 ml is for research purposes and 10 ml is for routine blood tests), and at the end of the trial (30 ml for research purposes). Please note the blood is not taken from your CRPS affected limb (unless in exceptional circumstances where we cannot reasonably get blood in another way). We will examine your research bloods for substances which may explain why you have CRPS, or which may help us to understand your condition better. The types of substances, which we may examine include, but are not limited to antibodies, cytokines and mediators. If you prefer not to provide blood samples for research, you can still participate in the clinical trial but we would still need to do the routine blood tests before your first infusion, to make sure there is no medical reason for you not to have the infusion.
- You will not have to stop any of your prescribed medications. Should you feel that the dose of your prescribed medications should be changed, we are asking you to please discuss this with your study doctor. This includes for example increases of your study medication in case of a flare up, or reduction of your study medication in case that you have less pain.

- You should preferably not start any new treatment for your pain during the study. If during the study you feel you need to seek a new treatment we ask that you speak to your study doctor first.
- Immunoglobulin may be less effective for the treatment of pain when patients develop a common cold or flu. Please avoid contact with friends or relatives who have a cold or flu if at all possible. However if you feel you have caught a cold or flu, please tell us. This will not exclude you from the study.

What are the alternatives for diagnosis or treatment?

- Pain such as yours may be amenable to an operation called 'Spinal Cord Stimulation', where an electrical lead is placed close to the nerves in your back. You should have discussed this option with your consultant or the study doctor before entering the trial.
- Physiotherapy is an important part of treatment for your condition and if you are seeing a physiotherapist you should continue this during the trial.

What are the side effects of any treatment received when taking part?

A. Side effects from the drug

A common side effect is an increase in the intensity of your pain. This may occur in up to 30% of patients both after immunoglobulin or the dummy drug. It rarely lasts longer than three days. Headaches are also common. Occasional side effects include short lasting nausea, vomiting and dizziness, chills, fever, nose bleed, a runny nose, tummy pain short-lasting back- and joint pains, coughing, low blood pressure and an allergic reaction such as a short-lasting skin rash. Rarely meningism can occur, that is an irritation of the lining of the brain causing severe headache.

With larger doses than used in this trial, very rare effects include acute kidney failure, and deep vein thrombosis (clotting of the deep veins in the leg). These latter side effects are not expected with the low dose being used in this trial.

Very rarely, a patient may develop a severe allergic reaction to the drug while the drug is infused. This can be a life-threatening situation, which may need immediate attention by your doctor.

Finally: The effectiveness of live vaccines such as measles, rubella, mumps and chicken pox may be reduced if you receive such vaccines within 3 months of receiving immunoglobulin treatment. For this reason, you should inform the investigator if you intend to have any vaccines during this time period.

Immunoglobulin is derived from human blood and there is a theoretical possibility of transmitting known or unknown infective agents, such as the hepatitis, AIDS and CJD (mad cow disease) viruses. There are no reports of any of the immunoglobulin being used in this trial causing any of these virus infections but the possibility cannot be completely excluded.

B. Side effects from intravenous infusion and blood donation:

The insertion of the needle or cannula for the infusion or blood donation may cause slight pain at the time and mild bruising afterwards. Please note we will not insert any needle or cannula into your CRPS-affected limb unless in exceptional circumstances where we cannot find another vein. Very rarely needle/cannula insertion might cause inflammation of the vein. Some people feel faint when they have an injection: please tell us if this applies to you and we will take special precautions.

We will provide a special space in your diary where we ask you to note any side effects, which you experience. If, after having received the drug, you have any concerns please contact your pain research centre and speak to the research doctor or nurse in working hours.

You will also be given an emergency contact phone number when you receive your first infusion at the Pain Clinic. This number can be used 24 hours a day in the case of a medical emergency, where your GP or another doctor needs to urgently know whether you have been given IVIG or the dummy medication.

What are the disadvantages of taking part?

Women who wish to take part must not be pregnant, or plan to become pregnant during the study. If you are at risk of becoming pregnant you must use an effective contraceptive during the course of the study. Appropriate methods of contraception include barrier contraception such as condoms or hormonal contraception such as the oral contraceptive pill. You may be asked to have a pregnancy test to exclude the possibility of a pregnancy. If any woman finds that she has become pregnant once starting the study she must tell her research doctor immediately.

Litigation: If you are in on going litigation with respect to the injury, which triggered your CRPS, and your trial infusion leads to strong on going pain relief and improved function, this might affect the level of compensation which you would receive for future losses.

Other trials: You will usually not be able to participate in other research trials within three months from the time of your second study visit – you would be able to participate in such trials thereafter. If you wish to participate in additional trials, please contact your study doctor.

What are the possible benefits of taking part?

You may get better with either immunoglobulin, or the dummy-drug. However, this cannot be guaranteed. The information we get from this study will help us and other researchers to understand and eventually treat your pain syndrome (CRPS) better.

What happens when the research study stops?

This is a research study. Should the treatment prove to be effective in this trial, we intend to pursue this research to make this treatment available under the NHS. However it will not be available in the near future.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research will be kept strictly confidential. Information held about you includes your medical history and your pain diaries and results from routine blood tests. Dr. Andreas Goebel, the Chief Investigator for this trial (XXXX) together with your study doctor will be responsible for safety and security of your data. Any information about you, which leaves the hospital will contain your initials and date of birth but will have your name, address and all identifiable information (including patient/ hospital/NHS number, and GP details) removed so that you cannot be recognised from it. Data from the study will be stored for at least 20 years with your name and address removed. Your GP will be notified of your participation in the trial if you agree to this.

What will happen to the results of the research study?

Results from this study are likely to be published in a medical journal. If you like you can obtain a copy of published results from your study doctor after the project has finished. If you are interested in feedback as to which treatments you received at which time, we will be able to tell you this after all patients have completed their treatment. You will not personally be identified in any report/publication.

Who is organising and funding the research?

This study is being organised by a team of pain researchers from across the UK, led by Dr Andreas Goebel. The IVIG is supplied by a pharmaceutical company (Biotest UK) and the placebo medication is manufactured by a NHS pharmacy. The Clinical Trials Unit at King's College London is helping with the trial.

The study is funded by the National Institute for Health Research under their EME research programme. Additional financial support is being provided by the Pain Research Foundation in Liverpool.

This is a doctor led study and no doctor or nurse will be paid personally for including you into the study

Reimbursement

We will pay reasonable travel expenses for you to travel to the research related appointments and if you need to be accompanied by a carer, we will also pay their travel

costs. If your travel expenses will be more than £50 per visit please advise us in advance. We will always try to make your visit possible and will also book a hotel for you if needed.

Who has reviewed the study?

The study has been reviewed by the NHS research ethics committee
East of England Hatfield REC (Formally known as: NRES Committee East of England – Welwyn) Room 002, TEDCO Business Centre, Rolling Mill Road, Jarrow, NE32 3DT

Contact for Further Information

In case of any further questions to this study, please do not hesitate to contact your study doctor.

Thank you for reading about this study.

STUDY PLAN:

PART ONE (ENROLMENT)

A First Appointment Time: 3 hours

1. The study will be explained to you in detail and you will be asked to sign a consent form at this stage. If you decide at any time that you do not wish to participate, you can change your mind.

2. You will be examined and asked some questions about your condition and medical history and details of any medications or treatments you currently receive.

3. You will be asked to complete some detailed questionnaires about how you are affected by your condition.

4. The feeling on your skin may be tested using a method called "quantitative sensory testing". This will be explained to you at the appointment and takes about 30min.

5. You will give blood as a gift for research purposes (if you have consented to do so) and for routine clinical testing (40ml, approximately 8 teaspoons).

6. If you are a woman of childbearing age, we will test your urine to exclude that you are pregnant. You should not become pregnant for the duration of this study.

7. First pain diary is given and explained to you
   You will be asked to complete the diary daily until your next appointment, and to telephone your study doctor in about 10 days time. He or she will decide if the study is suitable for you, based on your pain patterns and blood results. If so, an appointment will be made for you to receive IVIG or placebo infusion treatments. Before your appointment, a computer programme will decide which treatment you will receive, but neither you nor your doctor will know which you receive. You will be telephoned the day before your appointment to confirm you will definitely attend, as the pharmacy department will need to prepare the medication the day before your appointment.

8. You will be given the following instructions on the effects from your study medication, and on completing your pain diaries:
   - Both the study drug and the 'dummy drug' may provide important pain relief. We don't know why the dummy drug can provide important pain relief, but we have observed this in earlier trials. I.e. one cannot tell from the pain relief you experience whether you had the study drug, or the 'dummy drug'.

- Both the study drug and the 'dummy drug' may also cause an initial pain increase or other adverse symptoms such as headaches. I.e. one cannot tell from any adverse event you experience whether you had the study drug, or the 'dummy drug'.
- Any pain relief may last as little as a few days, or as long as a month, or even longer in some cases.
- It is important to the success of the trial, **that you record your pain accurately the way you feel it,** whether it is much pain, or little pain – what ever you record is equally valuable to the trial, as long as you record it as you feel it.

PART TWO (TREATMENT)

B Second Appointment (2-3 weeks after the first appointment)

Time: 6 hours in total
½ hour tests
4.5 hours 1st infusion
1 hour observation

1. You will be asked to complete some more detailed questionnaires, as you did on the previous visit.
2. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications
3. Your first dose of the study or dummy drug will be given to you through a cannula (a small needle) into your vein, over a period of 4.5 hours. Both before and after your infusion, and at regular intervals during the infusion, your blood pressure and pulse will be checked. During the infusion you are allowed to move around, go to the toilet, eat and drink.
4. Your second pain diary will be given and explained to you
5. The second appointment is over and you can leave after 1 hour. Because you may experience rare side effects such as nausea, which could interfere with your driving ability, you will not be able to drive a car home after this first infusion and you will need an escort to travel with you if you are walking or taking public transport. You are expected be able to drive as normal from the day after your infusion. If you feel well after your infusion, then for your next infusion in three weeks time you are not expected to need an escort, and you are expected to be able to drive.
6. The research nurse or doctor will speak to you by telephone twice in the next week to check if you are having any difficulties completing

your pain diary, and if you have any side effects or concerns you can discuss them during these telephone calls. You can also telephone the research nurse if you are worried about anything between appointments.

7. If you have a mobile phone, you will be texted every day from the day after this visit to the last study day, to remind you about the requirement to enter your average 24h pain intensity into your paper pain diary. You can opt out from this service. If you participate, you are encouraged to also text your average pain intensity to a free phone number especially set up for this trial once per day on each study day. If you have agreed to this, and we don't hear from you for a while we may call you to enquire whether everything is ok.

C Third Appointment (3 weeks after 2nd appointment) Time: 5.5 hours

1. You will be asked to complete some more detailed questionnaires, as you did on the previous visit.
2. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications
3. Your second dose of the study or dummy drug will be given to you through a cannula (a small needle) into your vein, over a period of 4.5 hours. During the infusion, your blood pressure and pulse will be checked regularly.
4. Your third pain diary will be given and explained to you
5. The third appointment is over and you can leave after 1 hour. You are expected to be able to drive a car home after this infusion, and you are expected to not need an escort should you choose to either walk or make use of public transport.
6. The research nurse or doctor will speak to you by telephone twice in the next week to check if you are having any difficulties completing your pain diary, and if you have any side effects or concerns you can discuss them during these telephone calls. You can also telephone the research nurse if you are worried about anything between appointments.

D After Infusions

1. You will continue on your normal pain medication**. Please note that between visit 1 and visit 4 you will not be able to start any new treatments for your pain. Such new treatments might**

interfere with the study and render the results worthless. However you can adjust your usual medications, should you need to. Your welfare always has priority. Should you feel, that you need to start new treatment for your pain, please contact the study team.

PATIENTS WHO CHOOSE **NOT** TO RECEIVE OPEN LABEL IVIG INFUSION (if you wish to receive the open label infusion, please go to section F):

E Fourth Appointment (3 weeks after last infusion) Time: 1 ½ hours

1. You will be examined again and asked to complete some more detailed questionnaires, as you did on the first visit, and if you had been tested with "quantitative sensory testing" on visit 1, this will be repeated now. You will also give 30ml of blood for research purposes if you have agreed to this (however you can withdraw your consent to give blood at any time).

2. If you are a woman of childbearing age, we will test your urine to exclude that you are pregnant.

3. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications

4. You will be asked to complete a simplified pain diary once a week for the next 3 weeks. At the end of the 3 weeks, the study nurse or doctor will speak to you by telephone to check this information but you will not need to attend the clinic again for the study. During this telephone call, you will also be asked about any new medications you may be taking or any changes to your usual medications and you will be asked about any side effects you may have experienced after the last infusion. If you have any ongoing problems, the research doctor or study nurse may wish to arrange to speak to you again. If not, this will be the end of the study. Thank you.

PATIENTS WHO CHOOSE TO RECEIVE 'OPEN LABEL' IVIG INFUSION

F Fourth Appointment (3 weeks after last infusion) Time: 6 hours

1. You will be examined again and asked to complete some more detailed questionnaires, as you did on the first visit, and if you had been tested with 'quantitative sensory testing' on visit 1, this will be repeated now. You will also give 30ml of blood for research purposes

if you have agreed to this (however you can withdraw your consent to give blood at any time). The blood can usually be drawn from the same vein through which you will receive your infusion (i.e. you will usually only require one puncture of your skin).

2. If you are a woman of childbearing age, we will test your urine to exclude that you are pregnant. You should not become pregnant for the duration of this study.

3. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications

4. Your first dose of the 'open label' IVIG will be given to you through a cannula (a small needle) into your vein, over a period of 4.5 hours. Both before and after the infusion, and a few times during the infusion your blood pressure and pulse will be checked

5. Your fourth pain diary will be given and explained to you.

6. The fourth appointment is over and you can leave after 1 hour. Because you may have received IVIG at this infusion for the first time, you will not be able to drive a car home after this first infusion and you will need an escort to travel with you if you are walking or taking public transport. You are expected be able to drive as normal from the day after your infusion. If you feel well after your infusion, then for your next infusion in three weeks time (should you decide to receive it) you are not expected to need an escort, and you are expected to be able to drive.

7. If you have any side effects or concerns you can telephone the research nurse between now and your next appointment.

8. If you decide at any time between now and 3 weeks from now *not* to receive a second open label infusion (see next section), we will then also sent you additional diaries to complete once a week through the post.

PATIENTS WHO CHOOSE TO RECEIVE SECOND 'OPEN LABEL' IVIG INFUSION

G Fifth Appointment (3 weeks after last infusion) Time: 6 hours

1. You will be asked to complete some more detailed questionnaires, as you did on the previous visit.

2. If anything has changed since your last appointment, we will need to know the details – for example if you have been unwell or seen your doctor or if you have started or stopped taking any medications

3. Your second dose of the open label IVIG will be given to you through a cannula (a small needle) into your vein, over a period of 4.5 hours. Both before and after the infusion, and a few times during the infusion your blood pressure and pulse will be checked

4. Your fifth set of pain diaries will be given and explained to you.

5. The fifth appointment is over and you can leave after 1 hour. You will be able to drive a car home after this infusion, and you will not need an escort should you choose to either walk or make use of public transport.

6. If you have any side effects or concerns you can telephone the research nurse between now and your next appointment.

7. The pain diaries you are given at this visit will be slightly different. You will now be asked to complete your pain diary as usual for 3 weeks and then you will be telephoned to check your pain levels. After that, you will be asked to complete your pain diary only once a week for another 9 weeks. The doctor or nurse will telephone you again when these diaries are complete to check the levels of pain. Both sets of diaries will be given to you today and you will not need to visit the clinic again for the research study. Twelve weeks after today's visit will be the end of the pain diaries and that will be the end of the study. Thank you.

General information on the return of Pain diaries

At the end of the study, although we will collect pain diary results by telephone, the pain diaries will also need to be returned by post (a stamped, addressed envelope will be provided for this) at the appropriate times. The research nurse or doctor will let you know when this needs to be done.

Thank you for reading about this study

Appendix 2 Consent form

[redacted]

[Print on hospital headed notepaper]

Centre Number: ***[insert centre number]***
Study Number:
Participant ID Number: ***[insert patient ID number]***

CONSENT FORM

Title of Project:
Low-dose Intravenous Immunoglobulin Treatment for Complex Regional Pain Syndrome (LIPS)

Name of Researcher: *[insert site principal investigator name]*

Please do not tick but initial the relevant box to confirm your consent.

I confirm that I have read and understand the information sheet, Version 3.0 dated 02.09.2013 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

1. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
2. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the study co-ordinating centre, the CLRN research network, representatives of the sponsor or the NHS trust, the ethics committee and regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
3. I agree to my GP being informed of my participation in the study. ☐
4. I understand that information held by the NHS may be used to keep in touch with me and follow up my health status. ☐
5. I agree to give a gift of research blood samples for the study (optional). If I do not wish to give a gift of blood samples for research I understand that I can still take part in the LIPS treatment trial. I understand that the research bloods will be used to research chronic pain conditions. ☐
6. I agree to receive daily text messages to my mobile phone reminding me both to enter my daily pain intensity into my pain diary, and to text my daily pain intensity to a free phone number (optional). ☐

Name of Participant	Date	Signature
Name of Witness (if patient cannot give written consent)	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Appendix 3 Research diagnostic criteria (the 'Budapest Criteria') for complex regional pain syndrome

General definition of the syndrome

Complex regional pain syndrome describes an array of painful conditions that are characterised by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

To make the clinical diagnosis, the following criteria must be met:

- Continuing pain, which is disproportionate to any inciting event.
- Must report at least one symptom in all four of the following categories:
    - sensory – reports of hyperaesthesia and/or allodynia
    - vasomotor – reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
    - sudomotor/oedema – reports of oedema and/or sweating changes and/or sweating asymmetry
    - motor/trophic – reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
- Must display at least one sign at time of evaluation in two or more of the following categories:
    - sensory – evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
    - vasomotor – evidence of temperature asymmetry (> 1 °C) and/or skin colour changes and/or asymmetry
    - sudomotor/oedema – evidence of oedema and/or sweating changes and/or sweating asymmetry
    - motor/trophic – evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
- There is no other diagnosis that better explains the signs and symptoms.

Appendix 4 Weight-determined dosing guide

Weight (kg) range	Dose (g) to be administered	Kits to be dispensed (ml)		Volume to be administered (ml)	Maximum hourly infusion rate (ml/hour)
		100	200		
35.5–45.4	20	–	2	400	88–113
45.5–55.4	25	1	2	500	113–138
55.5–65.4	30	–	3	600	138–163
65.5–75.4	35	1	3	700	163–188
75.5	40	–	4	800	188–213
85.5–95.4	45	1	4	900	213–238
95.5–105.4	50	–	5	1000	238–263
105.5–115.4	55	1	5	1100	263–288
115.5–125.4	60	–	6	1200	288–313
125.5–135.4	65	1	6	1300	313–338
135.5–145.4	70	–	7	1400	338–363
145.5–155.4	75	1	7	1500	363–388
155.5–165.4	80	–	8	1600	388–413

Appendix 5 Patient-recommended scale

1. How much use do you have of your limb overall?	0	Full use
	1	
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
	10	No use
	777	*Not available or not applicable*
	888	*Not done*
	999	*Unknown*
2. Can you move your limb_____ than before your treatment?	0	Much better
	1	Better
	2	Same
	3	Less
	777	*Not available or not applicable*
	888	*Not done*
	999	*Unknown*
3. Has lack of energy affected you/interfered with your activities over the last week?	0	Not at all
	1	
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
	10	Completely
	777	*Not available or not applicable*
	888	*Not done*
	999	*Unknown*

4. What was your average pain intensity *at rest* over the last week?	0	No pain
	1	
	2	
	3	
	4	
	5	
	6	
	7	
	8	
	9	
	10	Pain as bad as you can imagine
	777	*Not available or not applicable*
	888	*Not done*
	999	*Unknown*
5. Over the last week, has *movement* of your limb caused pain?	0	None
	1	Mild
	2	Moderate
	3	Severe
	777	*Not available or not applicable*
	888	*Not done*
	999	*Unknown*

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