

## Successful, and unsuccessful recruitment and retention strategies in a UK multicentre drug trial for a rare chronic pain condition which performed above target

Jatinder Bisla\*<sup>1</sup>, Gareth Ambler<sup>2</sup>, , Bernhard Frank<sup>3</sup>, Sumit Gulati<sup>4</sup>, Poppy Hocken<sup>5</sup>, Mairi James<sup>6</sup>, Joanna Kelly<sup>7</sup>, Jocelyn Keshet-Price<sup>8</sup>, Candy McCabe<sup>9</sup>, Deborah McGlynn<sup>10</sup>, , Nick Padfield<sup>11</sup>, David Pang<sup>12</sup>, Gill Pout<sup>13</sup>, Mark Sanders<sup>14</sup>, Mick Serpell<sup>15</sup>, Nicholas Shenker<sup>16</sup>, Karim Shoukrey<sup>17</sup>, Samuel Wesley<sup>18</sup>, Margaret Weston<sup>19</sup>, Beverly White-Alao<sup>20</sup>, Lynne Wyatt<sup>21</sup>, Caroline Murphy\*\*<sup>22</sup>, Andreas Goebel<sup>23\*</sup>

\*Corresponding Author

\*\* Senior Corresponding Authors.

1. \*Trial Manager. Kings College London Clinical Trials Unit, PO64, M2.06, Institute of Psychiatry, Psychology and Neuroscience, De Crespigny Park, London, UK, SE5 8AF. Tel: +44 207 848 0532; email: [jatinder.bisla@kcl.ac.uk](mailto:jatinder.bisla@kcl.ac.uk)
2. Associate Professor in Medical Statistics. Statistical Science, 1-19 Torrington Place, University College London, London, UK, WC1E 7HB. Tel: +44 20 7679 1878; Email: [g.ambler@ucl.ac.uk](mailto:g.ambler@ucl.ac.uk)
3. Consultant. Walton Centre NHS Foundation Trust, Liverpool L9 7AJ. Tel: +44 151 529 5749; email [bernhard.frank@thewaltoncentre.nhs.uk](mailto:bernhard.frank@thewaltoncentre.nhs.uk)
4. Consultant. Walton Centre NHS Foundation Trust, Liverpool L9 7AJ. Tel: +44 151 529 5749; email [sumit.gulati@thewaltoncentre.nhs.uk](mailto:sumit.gulati@thewaltoncentre.nhs.uk)
5. Research Nurse. Royal National Hospital for Rheumatic Diseases & University West of England , Bath, Somerset, Avon BA1 1RL. Tel: +44 01225 473 453; email: [poppy.hocken@nhs.net](mailto:poppy.hocken@nhs.net)
6. Research Coordinator. Queen Elizabeth University Hospital, Glasgow Clinical Research Facility, AFF1345 Govan Rd, Glasgow, UK, G51 4TF. Tel +44 141 211 3287; email: [mairijames@hotmail.com](mailto:mairijames@hotmail.com)
7. Strategic Data Management Lead KCTU. Kings College London Clinical Trials Unit, PO64, M2.06, Institute of Psychiatry, Psychology and Neuroscience, De Crespigny Park, London, UK, SE5 8AF. Tel: +44 207 848 0532; email: [joanna.kelly@kcl.ac.uk](mailto:joanna.kelly@kcl.ac.uk)
8. Senior Research Nurse. Norfolk and Norwich University NHS Trust, Colney Lane, Norwich, UK, NR4 7UY. Tel: +44 1603 288570; email: [jocelyn.keshet-price@nnuh.nhs.uk](mailto:jocelyn.keshet-price@nnuh.nhs.uk)
9. [Clinical Professor in Nursing](#). Florence Nightingale Foundation, London, University West of England, Bristol & Royal National Hospital for Rheumatic Diseases, Bath, Bath, BANES, BA1 1RL. Tel: +44 1225 465 941; email: [candy.mccabe@rnhrd.nhs.uk](mailto:candy.mccabe@rnhrd.nhs.uk) / [Candy.Mccabe@uwe.ac.uk](mailto:Candy.Mccabe@uwe.ac.uk)
10. Research Nurse. Queen Elizabeth University Hospital, Glasgow Clinical Research Facility, AFF1345 Govan Rd, Glasgow, UK, G51 4TF. Tel +44 141 211 3287; email: [Deborah.McGlynn@ggc.scot.nhs.uk](mailto:Deborah.McGlynn@ggc.scot.nhs.uk)
11. Consultant in Pain Medicine and Anaesthesia. Pain Management & Neuromodulation Centre, Guys & St Thomas' Hospital, London, UK, SE1 7EH. Tel: +44 207 188 3237; email: [Nicholas.Padfield@gstt.nhs.uk](mailto:Nicholas.Padfield@gstt.nhs.uk)/ [n.padfield@btconnect.com](mailto:n.padfield@btconnect.com)

12. Consultant in Pain Management and Anaesthesia. Pain Management & Neuromodulation Centre, Guys & St Thomas' Hospital, London, UK, SE1 7EH. Tel: +44 207 188 3237; email: [david.pang@gstt.nhs.uk](mailto:david.pang@gstt.nhs.uk)
13. Research Nurse. Norfolk and Norwich University NHS Trust, Colney Lane, Norwich, UK, NR4 7UY. Tel: +44 1603 288570; email: [gill.pout@nnuh.nhs.uk](mailto:gill.pout@nnuh.nhs.uk)
14. Consultant in Pain Medicine. Norfolk and Norwich University NHS Trust, Colney Lane, Norwich, UK, NR4 7UY. Tel: +44 1603 287 593; email: [mark.sanders@nnuh.nhs.uk](mailto:mark.sanders@nnuh.nhs.uk)
15. Senior Lecturer. Queen Elizabeth University Hospital, Glasgow Clinical Research Facility, AFF1345 Govan Rd, Glasgow, UK, G51 4TF. Tel: +44 141 211 3287; email; [michael.serpell@glasgow.ac.uk](mailto:michael.serpell@glasgow.ac.uk)  
[mgserpell@cheerful.com](mailto:mgserpell@cheerful.com)
16. Consultant Rheumatologist. Department of Rheumatology, Cambridge University Hospitals, Hills Road, Cambridge, UK, CB2 0QQ. Tel: +44 1223 217 457; email: [nicholas.shenker@addenbrookes.nhs.uk](mailto:nicholas.shenker@addenbrookes.nhs.uk)
17. Consultant in Anaesthesia and Pain Management. University Hospital of Leicester NHS Trust, , Leicester General Hospital, Gwendolen Road, Leicester, UK, LE5 4PW. Tel: +44 7879 495 33; email: [drshoukrey@yahoo.com](mailto:drshoukrey@yahoo.com)
18. Research Manager. Pain Management & Neuromodulation Centre, Guys & St Thomas' Hospital, London, UK, SE1 7EH. Tel: +44 207 188 3237; email: [Samuel.Wesley@gstt.nhs.uk](mailto:Samuel.Wesley@gstt.nhs.uk)
19. Administrator. University Hospital of Leicester NHS Trust, Leicester General Hospital, Gwendolen Road, Leicester, UK, LE5 4PW. Tel: +44 116 2586293; email: [Margaret.A.Weston@uhl-tr.nhs.uk](mailto:Margaret.A.Weston@uhl-tr.nhs.uk)
20. Trial Management Strategic Lead. Kings College London Clinical Trials Unit, PO64, M2.06, Institute of Psychiatry, Psychology and Neuroscience, De Crespigny Park, London, UK, SE5 8AF. Tel: +44 207 848 0532; email: [beverley.white@kcl.ac.uk](mailto:beverley.white@kcl.ac.uk)
21. Research Nurse. The Walton Centre NHS Foundation Trust, Lower Ln, Liverpool, UK, L9 7LJ. Tel: +44 151 529 5667; email: [lynne.wyatt@thewaltoncentre.nhs.uk](mailto:lynne.wyatt@thewaltoncentre.nhs.uk)
22. \*\* Operational Director. Kings College London Clinical Trials Unit, PO64, M2.06, Institute of Psychiatry, Psychology and Neuroscience, De Crespigny Park, London, UK, SE5 8AF. Tel: +44 207 848 0532; email: [caroline.murphy@kcl.ac.uk](mailto:caroline.murphy@kcl.ac.uk)
23. \*\*Reader and Honorary Consultant. University of Liverpool and Walton Centre NHS Foundation Trust, Liverpool L9 7AJ. Tel: +44 151 529 5749; email : [andreasgoebel@rocketmail.com](mailto:andreasgoebel@rocketmail.com)  
[andreas.goebel@liv.ac.uk](mailto:andreas.goebel@liv.ac.uk)

## Abstract

### Introduction:

Recruitment into trials in rare chronic pain conditions can be challenging so that such trials consequently are underpowered or fail.

### Methods:

Drawing from our experience in conducting, to date, the largest academic trial in the rare chronic pain condition, Complex Regional Pain Syndrome, we have identified recruitment and retention strategies for successful trial conduct.

### Results:

We present 13 strategies grouped across the categories of 'setting the recruitment rate', 'networking', 'patient information', 'trial management' and 'patient retention'. Moreover, 6 recruitment risks are also discussed. A conservative recruitment estimate, based on audits of newly referred patients to the trial centres without taking into account availability of 'old' patients or recruitment from outside centres, and assuming a 55% patient-refusal rate yielded accurate numbers.

### Conclusion:

Appreciation of these identified recruitment challenges and opportunities may contribute to supporting prospective investigators when they design clinical trials for chronic pain patient population groups where it has been historically difficult to conduct high quality and robust clinical trials.

## Background

More high quality trials in chronic pain conditions are desperately needed to advance patient care.<sup>1</sup> However the challenges of ensuring that a clinical trial recruits to target are well documented<sup>2</sup>. Some chronic pain conditions are rare, and the incremental recruitment challenges posed specifically by low prevalence figures have been discussed<sup>3</sup>. One of the most crucial consequences of poor recruitment is the potential for a trial to be under-powered leading in turn to a difficulty in detecting treatment effects and uncertainty in the validity of the results<sup>4,5</sup>. A 2015 analysis of registered trials showed that 19% of trials were closed or stopped early because of difficulties in accruing participants<sup>6</sup>. Furthermore, even where poor recruitment does not lead to trial stoppage, it can result in an extension of study timelines beyond planned enrollment periods with important adverse consequences to the drug development process<sup>7</sup>.

We have recently conducted the UK 'LIPS' trial, an academic phase III randomised controlled multicentre study of low-dose immunoglobulin (IVIG) treatment for persistent Complex Regional Pain Syndrome (CRPS)<sup>8</sup>. CRPS is a rare chronic pain condition typically affecting a distal limb after limb-trauma<sup>9</sup>. Pain persists in about 20% of patients, with serious consequences on their ability to

work, resulting in high costs to society<sup>10</sup>. The quality of life for these patients with persistent CRPS is very low<sup>11</sup>.

The LIPS trial has been the largest academic trial conducted in persistent CRPS to date. It was a parallel group study with an open-label extension, enrolling patients with CRPS of between 1-5 years duration, and with an average pain intensity of  $\geq 5$  on an 11-point numeric rating scale (NRS, 0='no pain', 10='pain as bad as you can imagine'). After a 2-week screening period, patients received 2 intravenous doses of immunoglobulin on days 1 and 22, or saline placebo; after 6 weeks they were offered up to two open treatments with IVIG. The primary endpoint was their pain intensity over days 6-42 after randomisation (37 daily pain intensity scores); this was compared between the two treatment arms (active and placebo). The trial protocol<sup>12</sup> and trial results have been published<sup>8</sup>.

The trial enrolled n=111 patients between 08.2013, and 10.2015, above the target of n=108 patients (Figure 1). Recruitment commenced in August 2013 at the lead centre and a delay in contract negotiations both at the lead centre, and at a number of recruiting centres resulted in an initially slower than anticipated rate of recruitment. However, recruitment targets were met within the 20th month and recruitment was ahead of target by the 23rd month of the recruitment window. This resulted in the trial over recruiting by 3 participants, (111 participants) and recruitment ending 3 weeks ahead of schedule. The last patient enrolment was 3 weeks *earlier* than projected. The retention of participants for the main part of the study was high with 98% of enrolled patients receiving one infusion, and 90% both infusions. (Table 1). Furthermore, compliance in completing the primary outcome measure was also high -106/111 (95%) of the randomised patients produced at least some primary outcome data; 98 of these were almost complete (34-37 days) and 8 were half complete (14-19 days), resulting in high data quality and confidence in the trial results.

Here we share recruitment and retention strategies which we found to be useful in our trial, with the aim of providing a resource for future investigators.

### **Figure 1**

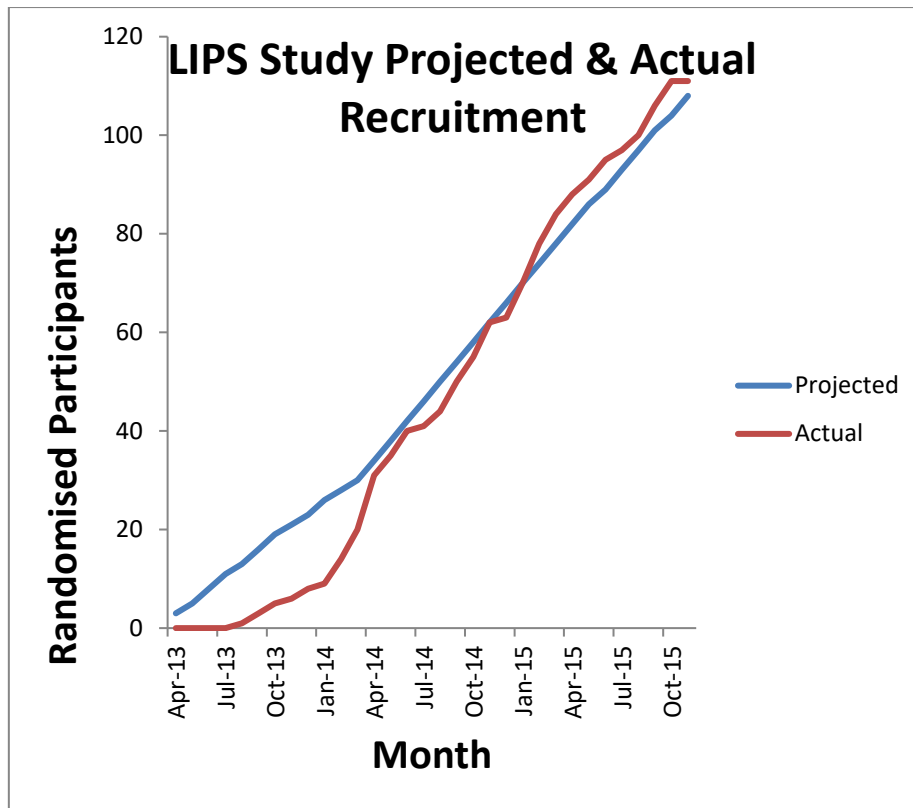


Figure 1. LIPS recruitment rate.

Table 1: Number of completed daily pain scores (days 6-42) for each patient by trial arm. IVIg=intravenous immunoglobulin

		Trial Arm	
		Placebo (n=56)	IVIg (n=55)
Number of recorded pain scores	(none)	3	2
	14		1
	15		1
	16	2	1
	17		2
	19		1
	34		1
	35	1	1
	36	9	5
	37	41	40

## Methods

After the LIPS trial completion and publication, the Chief Investigator and key team members at the collaborating Clinical Trials Unit (CTU) reviewed trial procedures. They discussed successful

strategies for patient recruitment and retention and considered these procedures within the context of prior experiences regarding clinical trial recruitment at the CTU, which is one of the largest CTUs within the UK. Thirteen recruitment and retention safeguards (5 safeguards for *setting the recruitment rate*, 1 for *networking*, 1 for *patient information*, 2 for *trial management*, and 4 for *patient retention*) were identified and graded, with \*\*\* indicating the highest perceived efficacy; six risks to recruitment were also identified. Consensus was achieved for all safeguards and risks.

## **RESULTS**

### **Setting the recruitment rate**

*Safeguard 1 Availability of data from an earlier pilot/feasibility study conducted in a similar population*<sup>13</sup>: Information on sample size; recognition of the enormous recruitment challenge in persistent CRPS even at a very large pain centre. \*\*\*

*Safeguard 2 Referral audit*: All six initially-scheduled trial centres were asked to record over 3 months the receipt of new clinical referrals of patients who would principally be suitable later to be approached for the LIPS trial. They were instructed to ignore any previously seen patients entered onto their databases or registries, even though during the trial they would be permitted to contact them; thus this procedure was designed to provide a considerable margin of tolerance. The same exercise was repeated about 1 year later, at the time of submission of a revised study grant application. Recruitment estimates for the trial were then based on these data, i.e. excluding any patients on databases.

The six centres received 46 referrals of potentially suitable patients during the two audit periods of overall 6 months. Applying the refusal estimate (see section 'refusal audit' below, 46x.45) we calculated that 20 patients would enrol during any 6 months period, an average of 3.3 patients/centre/6 months. This was 10% above the rate of 3 patients/centre/6 months required to recruit 108 patients (the patient number determined by the statistical analysis plan) over 36 months (see section 'balanced recruitment period' below); consequently the recruitment target was considered realistic, but with a relatively tight margin of error.\*\*\*

In the actual trial this recruitment estimate proved to be an accurate prediction of the real situation. There appeared to be variability between the accuracies in predicted recruitment amongst individual trial centres (Table 2). However, based on their respective audit results both strongly recruiting trial centres (Sites D and E) had initially in fact indicated a higher recruitment capacity than n=18, yet the respective local R&D departments had not wished for the site-PI's to commit to a larger number citing potential penalties for any under-recruitment. In both under-recruiting centres (Sites A and B) seasonal factors had been cited to explain in fact lower audit result figures, and the estimates had been upwards adjusted. Hence these observations further underline the validity of referral audit data in our context.

**Table 2**

<b>Site</b>	<b>Total Screened</b>	<b>Screen Fails</b>	<b>Total Recruited</b>	<b>Target</b>	<b>Percentage of Target</b>
A	11	1	10	18	55.5%
B	10	1	9	18	50%
C	19	1	18	18	100%
D	34	3	31	18	172.2%
E	30	2	28	18	155.5%
F	11	2	9	10	90%
G*	6	0	6	8	75%
<b>Total</b>	<b>121</b>	<b>10</b>	<b>111</b>	<b>108</b>	<b>103%</b>

**Table 2: Recruitment per trial-site** \*Site G was added after the initial planning period, see safeguard 'networking' below

*Safeguard 3 Refusal audit:* Based on experience in the preliminary trial<sup>13</sup> we estimated that 55% of otherwise seemingly eligible patients would refuse participation.

To confirm the validity of this estimate we contacted patients in two prospective study centres, A (n=6) and D (n=10). The respective ethics committees had confirmed that no ethics application would be required for this process and the respective R&D departments approved this approach. We provided these 16 patients with an abbreviated description of the study in lay language and asked, using a questionnaire, whether they would be interested to participate if they were

approached in the future. We encouraged return of questionnaires by post, and also contacted patients over the phone if there was no response.

The response was n=4 at site A (66%), n=9 at site D (90%). In an actual trial our experience is that virtually all patients can be reached, but this was not possible due to time limitations in this audit. Of the responding patients, 50% at Site A (n=2), and 78% at Site D (n=7) indicated that they would participate if such trial were to be offered. The reasons for refusal were prohibitive travelling potentially increasing limb pain (n=2), concern about IVIG being a blood product (n=1), and concern that the study drug won't be available after study completion (n=1); with regards to the latter several patients mentioned, however, that their *positive* indication for participation (i.e their non-refusal) was, in part influenced by the fact that our study design would allow them to try the active drug in the trial extension phase. We thus considered that the estimated proportion of 55% refusing patients was valid. \*\*\*

The refusal audit also highlighted the importance of choosing the most appropriate patient approach method: while at Site A the patient approach had been conducted by a Research Nurse with minimal background knowledge about CRPS, at Site D the approach was made by a Doctor with expertise in CRPS. Upon commencing the trial all study team members who approached patients received in-depth study specific training which may have contributed to the relatively low screen fail numbers at all sites (Table 2). An alternative interpretation of the low screen-fail data is that the inclusion criteria for the trial were sufficiently broad, which would in turn support good generalisability of the results.

*Safeguard 4 Balanced recruitment period:* The statistical sample size calculation indicated that 108 patients would be required to achieve 90% power to detect a clinically important difference in pain score of 1.2 points at the 5% significance level<sup>12</sup>. From this, we determined a recruitment period of 36 months taking into account data from preliminary audits described above and striking a balance between i) the risk that alternative treatment strategies might emerge during the trial potentially threatening recruitment - and increased trial costs with a longer duration, and ii) the limit posed to the recruitment rate for this rare condition. We calculated a target recruitment rate of 108/36=3 patients per month (18 patients per half year).\*\*

*Safeguard 5: Use of patient-registries:* At two trial sites, hospital-approved CRPS patient-registries held names and identification numbers of all patients with CRPS seen at the respective clinical services over the past few years. These patients had either explicitly or implicitly agreed that they can be contacted for research purposes provided certain data protection procedures were followed. Other PI's had collected names of potentially suitable patients seen by them since the start of the LIPS consultation process.\*\*

### **Use of Research Network**

*Safeguard 6: National Institute for Health Research (NIHR) Clinical Research Network (CRN) registration:* In England, costs for such study procedures which are expected to be delivered through National Health Service (NHS) resources, such as identification of participants via the screening of a NHS record, recruitment of participants including consent and any procedure that is carried out for safety purposes, will be funded by 'Local Clinical Research Networks' (LCRNs). All studies that have met the eligibility criteria are adopted onto the NIHR Portfolio which is a database of studies; LIPS was one of these studies



(<https://www.nihr.ac.uk/research-and-impact/nihr-clinical-research-network-portfolio/>). These studies are also listed within the UK Clinical Trials Gateway (<https://www.ukctg.nihr.ac.uk/home/>) and potential recruitment sites and investigators throughout the UK can scan this study-registry looking for new study opportunities. These sites may then contact the study trial management group offering participation. This process is considered a win-win situation for the UK research environment as it ultimately facilitates recruitment. The LIPS trial management group was contacted early after study setup by the Site G trials unit, and following further feasibility checks it was decided that there was sufficient potential for the local PI to enrol eight patients at Site G. Site G was introduced as a 7<sup>th</sup> trial centre, which took pressure off the slim recruitment margin highlighted above.\*\*

### **Patient information**

*Safeguard 7 Coherent patient information and education:* A ten minute video was recorded by the CTU team. The ethics committee had approved the use of this video. The Chief Investigator (AG) explained purpose and background of LIPS; the video was shown to each patient at their screening visit. It was hoped that this would deliver coherent information about the trial.

The video also included educational elements, for example patients were advised that we would not gain if patients ‘made up’ good results perhaps out of a wish to please us (‘participant bias’ or ‘response bias’)<sup>14</sup>, and why this would in fact be counter-productive; the main message was patients should simply indicate whatever they felt, and that this would be exactly right for the trial. During the trial the CI became aware of another type of response bias not addressed by this video or in another way – patients anecdotally reported that they would feel embarrassed if they were reporting excellent pain relief while in the placebo arm.

### **Trial management**

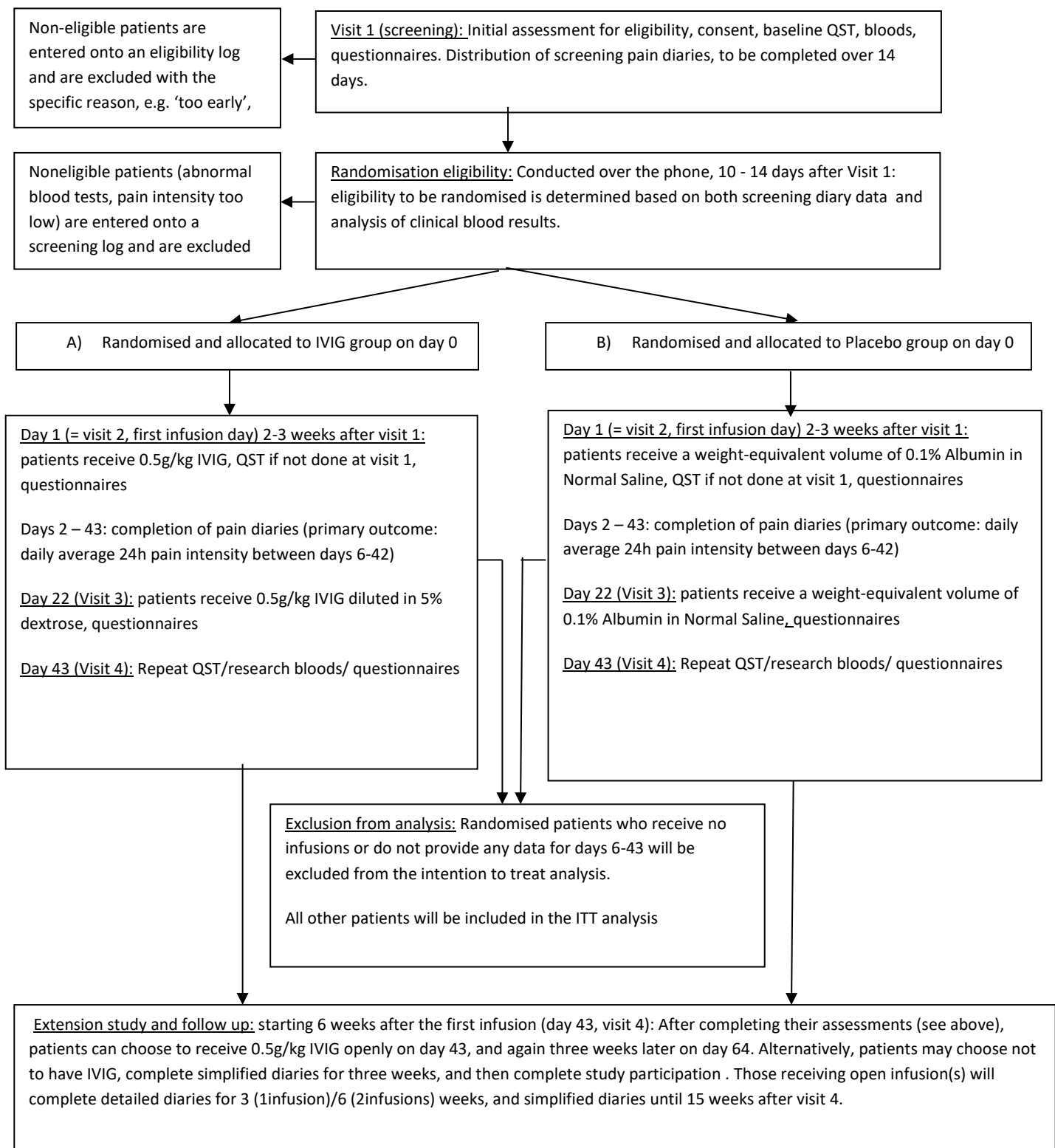
*Safeguard 8 CI Oversight:* The CI followed a ‘hands-on’ approach; he attended and contributed to weekly trial management and recruitment teleconferences and instigated frequent communication with the 6 site-PI’s and their teams. Perceived issues were addressed; particularly, lower than expected enrolment occurring at any site was flagged up and discussed with the respective team, thus allowing the local management team to help analyse causes and to put forward suggestions.\*\*\*

*Safeguard 9 Involvement of an experienced CTU:* The involvement of an experienced CTU ensured that the protocol was sufficiently detailed, and that trial processes such as oversight committee and trial management group meetings were appropriately laid out so that procedures to address any recruitment delays were in place. It also meant that during periods of staff sickness or absences in the co-ordinating team, experienced senior staff within the CTU were able to fill manpower gaps until those were resolved.\*\*\*

**Patient retention**

*Safeguard 10 Study design involving a relatively short blinded study period (6 weeks), and inclusion of an open extension phase.* (Figure 2) These two study-design features may have resulted in an improved retention of those patients perceiving no benefit in the randomised phase (see also Safeguard 3, *refusal audit*, above).\*\*\*

**Figure 2. Participant Flow Chart across the LIPS Study Timelines**



**Safeguard 11 Patient involvement:** In preparation for the grant application (NIHR), an early study protocol version was sent to patients with CRPS, and feedback was 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. They were a subgroup of participants in the 'Liverpool CRPS pathway group', a regional patient support group. Suggestions related mostly to the convenience of attendance and the inclusion of additional outcomes – these were implemented. For example, the time-windows around the infusion dates were widened to meet patient concern about scheduling their travel. Patient information sheets were reviewed for acceptability by the same Liverpool patient group. A patient representative with a history of CRPS volunteered to join the trial steering committee and regularly attended meetings and offered advice and guidance throughout the trial. We think that these PPI elements have contributed to make the trial 'service-user friendly', particularly as we realised the burden of travel on this patient group. \*\*

**Safeguard 12 Phone calls:** Patients were contacted per phone during the trial at set time points with one main objective to ensure adherence; we suggest that this measure contributed to achieving a high level of completed data and few drop outs (Table 1).\*\*

**Safeguard 13 Generous travel reimbursement:** The participants travel-expenses were not capped at a set level although an upper limit guidance was provided; expenses above that limit were approved by the Chief Investigator on an individual case by case basis. Additionally, expenses were reimbursed promptly by the research site and then invoiced back to the study. For more lengthy and expensive journeys, taxis were organised by the respective study nurses, which were paid for on account so that the participants had no initial financial outlay to attend study visits. Carer travel costs were also reimbursed as many participants could not travel alone.\*

**Unsuccessful approaches designed to support recruitment and retention:**

*Half-yearly adverts (1/4 page) in the professional journal of the British Pain Society ('Pain News') served as referral prompts throughout the UK; presence with a poster on one British Pain Society Congress; twitter; UK Pain Fellow's online group (a 'google group' for Doctors in training in pain medicine); contact of UK patient organisations; invitation of certain pain centres with a suspected or known interest in CRPS care to become patient identification centres (PICS) with consequent establishment of 9 such centres as PICS (with promise to include all PICS PIs into a secondary outcome publication who successfully identify at least 1 patient who would subsequently be enrolled); contact of all UK pain centres once per year with addresses obtained through a national audit of all UK pain management institutions; registration on national or international registries (ISRCTN, ICTRP, EUDRAC) - these approaches did not measurably help recruitment.*

No patients were enrolled following referral from a PIC site. One issue identified was the often long travel that was required from the area of the PIC site where a patient lived to a trial site. Similarly, only one patient was enrolled following referral from other (non PICS, non CRPS-specialising) pain clinics, even though we were grateful that such referrals were regularly received – strict enrolment criteria may have played a role.

A steady stream of patient self-referrals/enquiries did also not lead to any recruitment – in part because strict diagnostic criteria for CRPS were applied. Recruitment attempts through the national CRPS registry did not yield any recruits, likely as many patients on this registry have very

longstanding CRPS exceeding the LIPS upper disease duration cutoff 5 years<sup>15</sup>, and also since some of these patients had already been contacted directly by those centres who had originally put them onto that registry; the 3 largest of these centres were part of the trial.

*Text Messaging Service (TMS)*: Introduced as both a retention strategy and a secondary primary data collection source. It was envisaged that TMS would keep participants engaged in the trial as they would receive a daily reminder text, and that this would maximise data quality (primary outcome, pain intensity – daily reminders to complete diaries and text the score back) when used in parallel with the paper diaries. The system was somewhat cumbersome to set up and run, so that implementation at the sites was slow. In addition, over time the trial team became aware of excellent completion rates with the paper diaries, so that this system was abandoned after the first recruitment year .

### **Risks to recruitment and retention**

We identified risks; most of these (i-v) related to the specific study population suffering from a severe chronic pain condition:

- i) patient concern about pain exacerbation with travel – determined by the distance to the closest trial centre and the number of visits needed
- ii) patient fear of potential pain increase with the intervention
- iii) patient concern about commitment on the background pain flares ('if my pain is bad I would not be able to travel').

Measures to address these issues (i-iii) included trial-design adaptations to minimise the number of visits, good geographical spread of trial sites, and introduction of more flexibility in the study visit times.

- iv) patient unfamiliarity with their respective PI - patients appeared more motivated if they knew their respective PI from prior clinical encounters
- v) prior pain management program (PMP) attendance - chronic pain is a biopsychosocial condition. Patients who had previously attended a PMP appeared less distressed about potential side effects, in fact our impression was that they may have reported less side effects (although we did not measure this) because they had a better understanding about their own condition including its inherent flare up's. We thought that patients who had not attended a PMP needed more support in their consideration about continuation with the trial if they encountered any adverse circumstances.
- vi) Contract negotiations were outside the trial teams' control. Recruitment at the lead site started relatively early, but there was a delay at most other sites, leading to initial recruitment below plan (Figure 1).

**Table 3**

<i>Safeguard Theme</i>	<b>No.</b>	<b>Title</b>
<i>Setting the recruitment rate</i>	Safeguard 1	Availability of a pilot study
	Safeguard 2	Referral audit
	Safeguard 3	Refusal audit
	Safeguard 4	Balanced recruitment period
	Safeguard 5	Use of patient registries
<i>Networking</i>	Safeguard 6	Research Networks
<i>Patient information</i>	Safeguard 7	Screening Video
<i>Trial management</i>	Safeguard 8	CI oversights
	Safeguard 9	Experienced CTU
<i>Patient retention</i>	Safeguard 10	Open treatment period
	Safeguard 11	Patient design involvement
	Safeguard 12	Phone calls
	Safeguard 13	Travel reimbursement

**Table 3:** *Recruitment and retention safeguards.* CTU= Clinical Trials Unit**Discussion:**

Drawing from the experience in this - to date the largest academic trial in the rare chronic pain condition, Complex Regional Pain Syndrome, we have outlined 13 recruitment strategies for successful trial recruitment. There were 5 strategies in the categories '*setting the recruitment rate*', 1 in '*networking*', 1 '*patient information*', 2 '*trial management*', 4 '*patient retention*' (Table 3).

The importance of planning is obvious. Based on challenges to recruit into earlier trials in this condition, we estimated recruitment numbers in an apparently conservative way. For example, we conducted 2 referral audits at each trial centre to gauge the numbers of newly referred, potentially suitable patients, and we conducted a patient refusal audit; we then based our recruitment estimate per site on the number of newly referred patients and a generous refusal rate, without taking into account any patients seen previously at the trial centres, whose details had been entered on internal databases and who would later be contactable. We note, that while recruitment was successful, we were just 3 weeks 'better' than our target, which also highlights that this conservative approach was critical. A more optimistic approach based on these same audit numbers, but also taking into account patients on internal databases would have at least doubled the recruitment estimate, with consequent failure to recruit to target.

We have also highlighted 6 recruitment risks, most of which are specific to the group of patients with moderate or severe chronic pain, see Results section. We would like to emphasize the potential benefits of including patients into analgesia trials, who have attended a multidisciplinary pain management program. Having chronic pain is usually a distressing experience, and where unexpected

drug side effects, or flare-up's of the pain condition occur during participation in a trial, patients who have acquired techniques to manage their condition may find it easier to put these effects into perspective and adhere to the trial protocol as appropriate. We would like to suggest that more research in this area will be crucial to the development of recruitment strategies for chronic pain trials in the future, particularly where drugs with an unknown safety profile in a pain population are being assessed. Independently, a risk not addressed in this trial was potential response bias due to a patient sense of possible de-validation if they reported good pain relief while receiving placebo. This type of bias may be particularly relevant in academic trials such as our where patients know their investigators also clinically; this may need to be addressed in future patient education efforts.

A limitation to our report is that we did not examine the impact of patient inclusion/exclusion criteria on the LIPS recruitment rate; narrow criteria may increase screen failure rates and hence slow recruitment. We note that the low screen failure rate in LIPS (table 2) is likely reflective of undocumented, effective pre-screening by study investigators based on clinical notes or recall taking place *before* patients were invited to attend for screening; available data do therefore not allow us to investigate this important factor further.

Additional recruitment strategies *not* utilised by us include enlistment of international trial centres, and extension of the trial recruitment period. The prior strategy was extensively used in a recent successful *commercial* trial in trigeminal neuralgia, another rare chronic pain condition, upon recognition that the original recruitment-estimates would not be achieved<sup>16</sup>. However, it may be challenging to employ this strategy in *academic* trials because the costs for establishing and monitoring sites abroad are often not covered by academic trial-grant agreements; similarly, extension of the recruitment period incurs additional staffing costs, and in the UK such costs are generally not being covered by public research funding bodies. We made only minimal use of social media, and we did not use primary care databases, strategies which are increasingly employed in other studies.

In summary, we have presented 13 recruitment strategies and 6 recruitment risks identified from a successful randomised controlled trials in a rare chronic pain condition. It is hoped that the findings may contribute to supporting prospective investigators when they design such trials.

## References

1. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain* 2010;149:177-93.
2. Treweek S, Lockhart P, Pitkethly M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ Open* 2013;3.
3. Zakrzewska JM, Palmer J, Bendtsen L, et al. Challenges recruiting to a proof-of-concept pharmaceutical trial for a rare disease: the trigeminal neuralgia experience. *Trials* 2018;19:704.
4. Gul RB, Ali PA. Clinical trials: the challenge of recruitment and retention of participants. *J Clin Nurs* 2010;19:227-33.
5. Fisher L, Hessler D, Naranjo D, et al. AASAP: A program to increase recruitment and retention in clinical trials. *Patient Education and Counseling* 2012; 86: 3 372-377.
6. Huang GD, Bull C, McKee KJ, et al. Clinical trials recruitment planning: A proposed framework from the Clinical Trials Transformation Initiative. *Contemporary Clinical Trials* 2018; 66: 74-79

7. Campbell MK, Snowdon C, Francis D, et al. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. *Health Technol Assess* 2007;11:iii, ix-105.
8. Goebel A, Bisla J, Carganillo R, et al. Low-Dose Intravenous Immunoglobulin Treatment for Long-Standing Complex Regional Pain Syndrome: A Randomized Trial. *Annals of internal medicine* 2017;167:476-83.
9. Harden RN, Bruehl S, Perez RS, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. *Pain* 2010/8;150:268-74.
10. Scholz-Odermatt SM, Luthi F, Wertli MM, Brunner F. Direct Health Care Cost and Work Incapacity Related to Complex Regional Pain Syndrome in Switzerland: A Retrospective Analysis from 2008 to 2015. *Pain Medicine* 2019, 0(0), 2019, 1–11
11. Kemler MA, de Vet HC. Health-related quality of life in chronic refractory reflex sympathetic dystrophy (complex regional pain syndrome type I). *J Pain Symptom Manage*. 2000 Jul;20(1):68-76.
12. Goebel A, Shenker N, Padfield N, et al. Low-dose intravenous immunoglobulin treatment for complex regional pain syndrome (LIPS): study protocol for a randomized controlled trial. *Trials* 2014;15:404.
13. Goebel A, Baranowski AP, Maurer K, Ghiai A, McCabe C, Ambler G. Intravenous Immunoglobulin Treatment of Complex Regional Pain Syndrome: A Randomized Trial. *AnnInternMed* 2010;152:152-8.
14. Furnham A. Response bias, social desirability and dissimulation. *Personality and Individual Differences* 1986;7 385-400.
15. Shenker N, Goebel A, Rockett M, et al. Establishing the characteristics for patients with chronic Complex Regional Pain Syndrome: the value of the CRPS-UK Registry. *British journal of pain* 2015;9:122-8.
16. Zakrzewska JM, Palmer J, Morisset V, et al. Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial. *Lancet neurology* 2017;16:291-300.