

Are you better? A multi-centre study of patient-defined recovery from Complex Regional Pain Syndrome.

RUNNING HEAD: Defining recovery from Complex Regional Pain Syndrome

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ABSTRACT

Background: Complex Regional Pain Syndrome (CRPS) symptoms can significantly differ between patients, fluctuate over time, disappear or persist. This leads to problems in defining recovery and in evaluating the efficacy of therapeutic interventions.

Objectives: To define recovery from the patients' perspective and better understand their priorities for treatment approaches.

Methods: Establishing an international consortium, we used a 2-Round Delphi-based study in eight countries across Europe and North America. Participants ≥ 18 years who met, or had met, Budapest clinical criteria were included. Round 1 participants completed the statement: "I would/do consider myself recovered from CRPS if/because..." alongside demographic and health questionnaires. Data were thematically organised and represented as 62 statements, from which participants identified and ranked their recovery priorities in Round 2.

Results: Round 1 (N=347, 80% female, 91% non-recovered) dominant ICF themes were: activities of daily living; bodily functions; external factors; participation and personal factors. The top 5 priority statements in Round 2 (N=252) were: no longer having 1) CRPS-related pain, 2) generalised pain and discomfort, 3) restricted range of movement, 4) need for medication, 5) stiffness in the affected limb. With very few exceptions, priorities were consistent, irrespective of patient demographics/geography. Symptoms affecting daily activities were among those most frequently reported.

Conclusions: Our data showed a small number of themes are of highest importance to CRPS patients' definition of recovery. Patients want their pain, movement restriction and reliance on medication to be addressed, above all other factors. These factors should therefore be foremost concerns for future treatment and rehabilitation programmes.

Statement of significance:

- Those with longstanding CRPS may no longer meet diagnostic criteria but still be symptomatic.
- Defining recovery is therefore problematic in CRPS.
- Our study has identified patients' definition of recovery from CRPS, in order of priority, as relief from: their CRPS-related pain, generalised pain, movement restriction, reliance on medication, and stiffness.

1. INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a pain condition diagnosed using validated clinical diagnostic criteria known as the Budapest criteria (Harden et al., 2010). Signs and symptoms are usually limited to a single limb, which may include oedema, altered hair and nail growth, sensory, motor and autonomic disturbances (Harden et al., 2010). In addition, disrupted body perception and dis-ownership of the affected limb are commonly described (Frettlöh et al., 2006; Galer et al., 1995; Galer and Jensen 1999; Lewis et al., 2007; Moseley 2005). Symptoms usually develop following trauma to a limb but very rarely can occur spontaneously (Birklein and Schlereth 2015; Stanton-Hicks et al., 1995).

For the majority, CRPS resolves within a year, but prospective studies have indicated severe pain remains for 13% of patients ≥ 1 year after diagnosis (Zyluk 1998) and stiffness continues to affect up to 65% (Bickerstaff and Kanis 1994). Evidence synthesis of longer term retrospective studies report the persistence of symptoms for between 22% and 64% of patients ≥ 3 years after diagnosis (Bean et al., 2014a). Unremitting symptoms in CRPS are associated with long-term disability, poor psychological health and reduced quality of life (QoL) (Field et al., 1992; Geertzen et al., 1998; Kemler and de Vet 2000; Lohnberg and Altmaier 2013).

The trajectory of long-term CRPS is not straightforward and signs and symptoms fluctuate over time. While many of the initial florid presenting features of CRPS may dissipate, patients may remain far from their premorbid health state (Birklein and Schlereth 2015; Frettlöh et al., 2006; Hush et al., 2009; Lewis et al., 2007). In this scenario, defining recovery from CRPS, evaluating the efficacy of therapeutic interventions, and setting inclusion criteria for clinical studies becomes problematic.

Patients' experience of chronic pain is moderated by multiple psychosocial, behavioural and physiological factors (Dansie and Turk 2013; Hush et al., 2009), and "recovery" is an individual construct, dependent on idiosyncratic appraisal of the impact of symptoms on daily activities (Hush et al., 2009). People adjust to accommodate their changed health status, leading to "response-shift": a recalibration, re-evaluation or reprioritisation of health standards (Sprangers and Schwartz 1999). This can confound traditional pre- and post-intervention assessments (Osborne et al., 2006). Furthermore, where there may be limited physical signs of an obvious cause of persistent pain and disability, such as long-term CRPS, "recovery" is a far from simple construct (Beaton et al., 2001).

Recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) promote patient-centred research, and advocate allowing patients to describe what is important to them when defining recovery (Dworkin et al., 2008).

To achieve a comprehensive understanding of patient-defined recovery, and the factors that influence this, an international consortium was established in 2012 comprising patients, clinicians and academics from eight countries across Europe and North America. Consortium members either had

research or clinical expertise in CRPS, relevant methodological expertise, or could represent the patients' perspective for this condition. We present here findings from a 2-Round Delphi-based study aiming to define recovery from CRPS from the patients' perspective.

2. METHODS

2.1. Ethical approvals and funding

UK National Health Service (NHS) Ethical and Research and Development approvals were obtained for the study as a whole, and within this, individual centres obtained local institutional and health services approvals. All approvals were seen by the lead centre (UK) prior to data collection commencing. In addition, participants recruited from pre-existing site specific, or country specific, registries and databases had given prior consent to be contacted for future research purposes. Participants' consent was otherwise assumed by the return of completed questionnaires.

2.2. Development of study protocol

Five workshops were convened between July 2012 and January 2015 (see Figure S1). All workshops were conducted following a structured format with clear aims, objectives and specified methodological formats. All decisions were subject to majority consensus between workshop attendees. Further details of each workshop are given below.

2.2.1. Workshops

Workshop 1:

Within this workshop the theoretical, ethical and methodological frameworks for the study and content of the Round 1 study questionnaires (quantitative and qualitative) were agreed. Standardised patient-reported outcome measures were identified, and questions developed to investigate participants' definitions of recovery.

Workshop 2:

A structured 2-day skills workshop was held for a core team of Expert Patient Researchers and academic researchers, to ensure competence and consistency in the qualitative data analysis approach. The Consortium agreed to use the World Health Organisation's (WHO) International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2001) framework to guide coding categorisation (Figure S2). This framework had previously been used successfully by RP and FB (Boogaard et al., 2011; Brunner et al., 2008; Brunner et al., 2010).

Workshop 3:

Within this workshop, recruitment activity and data collection to date were discussed and consensus reached how the coding framework would be applied for the on-going qualitative data analysis. Consortium members assessed and confirmed the standardisation of the initial coding using early Round 1 qualitative data.

Workshop 4:

This was held to review the emergent themes from the qualitative analysis of the Round 1 data and to agree the wording and analysis strategy for Round 2 data. Consortium members reached consensus about which statements comprehensively represented patients' perceptions of recovery and the content of the Round 2 questionnaires.

Workshop 5:

Full qualitative results from Round 1 were presented, and findings from preliminary analyses of the quantitative data were reviewed. A strategy was agreed for further data analysis and dissemination of all study findings.

2.3. Study participants

Potential participants ≥ 18 yrs who had met the Budapest CRPS diagnostic criteria (Type 1 or Type 2, confirmed by clinical records) (Harden et al., 2010) were identified from 8 country-specific CRPS databases or clinic-specific research lists: UK (Bath), Germany (Mainz; Erlangen, Fürth), USA (Chicago), Canada (Toronto; Longueuil, Quebec), Switzerland (Zurich), Denmark (Aarhus), the Netherlands (Trauma RElated Neuronal Dysfunction (TREND) Consortium) and Poland (Pomerania). Participants were included if they were able to understand the written documents, as subsequently indicated by return of a completed questionnaire. (Documents were provided from each study centre in the language concordant with what was spoken in that country. See section 2.4.3.) Exclusion criteria were a diagnosis of CRPS following any cerebrovascular problems or cardiac event.

To achieve a more or less equal distribution of relevant patient characteristics across countries, and taking into account that we wanted to be able to form strata based on gender, age (3 groups), disease duration (3 groups) and employment status (yes/no), we aimed to recruit 36 patients per country. With 9 countries (we counted Canada as 2, because the two institutes are in different language areas), this totalled 324 patients. Considering a non-response rate of 50%, we calculated we would have to send out at least twice this number of questionnaires. We ultimately sent out questionnaires to 679 potential participants.

Each centre was responsible for local recruitment, with purposive sampling used to capture a range of disease durations and employment statuses (Mays and Pope 2000). Potential participants were sent a letter of invitation by post, except for newly diagnosed patients (≤ 1 year CRPS duration) not yet recruited to a CRPS database. In these cases, eligibility was determined by a member of each site's clinical team, and a letter of invitation was provided to participants when attending that site's outpatient clinic. Individual centres were responsible for all data collection from participants they recruited.

Only those participants who completed Round 1 documentation were potential study participants for Round 2 of the study.

2.4. Procedure

2.4.1. Round 1

The invitation mailing included: a Round 1 questionnaire pack (Part A and a sealed envelope containing Part B); an envelope for the completed Part A questionnaires; and a pre-paid envelope for the return of all completed documents. Part A questions asked for demographic information (date of birth, gender, employment status, years of formal education, limb affected, hand dominance); participants' perception of what stage they were in the disease (early, late, recovering, recovered); whether they had CRPS type 1 or 2 (with no, or known, major nerve damage respectively); the date the patient believed the CRPS symptoms started; and whether they cared for other family members inside/outside of the home. Participants were asked to indicate if they considered themselves a) not recovered from CRPS, b) partially recovered from CRPS or c) fully recovered from CRPS. Instructions against responses to a) or b) asked participants to answer the open question in fewer than 100 words: "I **would** consider myself recovered from CRPS if". Where participants indicated c) (they had recovered from CRPS), instructions asked them to answer: "I **do** consider myself recovered from CRPS **because**"

Part B questions asked: the date the participant's CRPS commenced; whether the CRPS symptoms were related to trauma or were spontaneous; and what other health conditions affected the participant's life. To give an indication of disease status, participants were asked to indicate which symptoms (from a list of fifteen derived from the Budapest CRPS criteria) they had experienced in the prior 48 hours. They were also asked to complete a number of standardised health outcome questionnaires, further details of which are given below in section 2.4.3.

Written instructions made it clear to participants that they should complete the Part A questionnaires and seal their responses in the envelope provided before opening the envelope containing Part B and completing the questionnaires contained inside. This was to ensure that responses to the open-ended question were not prejudiced by completion of the standardised health questionnaires. However, as questionnaires were completed in patients' homes, we had to rely on their voluntary adherence to this protocol. Participants were asked to return all questionnaires to their local study centre in a provided prepaid envelope within two weeks of the date of their letter of invitation.

Study questionnaires had been pre-tested with a small number of patients in the UK and the USA for usability and modified as required prior to ethical approvals being obtained. All questionnaire packs, irrespective of language or study centre, were printed and compiled in the lead (UK) centre for consistency, prior to posting to each recruitment site.

2.4.2. Round 2

Derived from responses to the open question in Round 1 (as described above), participants who had submitted completed questionnaires were presented with 62 statements relating to perceptions of recovery (see Results). These statements had been listed in random order and translated as necessary. Added to this was a further statement (number 63): "I do not find any of these statements important with regards to my recovery from CRPS". Participants were asked to complete the statement: "My idea of recovery from CRPS is...." by selecting, from the statements, the 10 they felt were most relevant to their idea of recovery from CRPS. A minimum of 3 statements was specified for those who felt unable to select 10. Participants were then asked to rank their selected statements in order of relevance (where 1 = most relevant, 2 = second most relevant and so forth). The standardised health outcome questionnaires (see section 2.4.3) used in Round 1 were also repeated in Round 2.

2.4.3. Standardised health outcome questionnaires:

The Radboud Skills Questionnaire (RASQ) (Oerlemans et al., 2000) (for those with upper limb CRPS only) is a self-report questionnaire of upper limb physical function in CRPS. It contains items representing the 'disabilities due to hand disease' domain, of the Dutch elaboration of the International Code of Impairments, Disabilities and Handicaps. The RASQ questionnaire comprises 45 items across 11 categories, including personal care, domestic and other activities.

The Measuring Activity Limitations in Walking Questionnaire (v.5) (Roorda et al., 2004) (for those with lower limb CRPS only) is a self-administered questionnaire, appropriate for all age groups living at home with lower-extremity disorders. Items ask patients about what they can actually do, rather than what they think they can do, in terms of walking. Not all of the 41 items are required (Roorda et al., 2005) and 35 items relating to walking at home and walking outside were selected for use in the present study, with permission from the developer.

The Short Form McGill Pain Questionnaire (Melzack 1987) is a self-report questionnaire providing a comprehensive assessment of subjects' pain. It includes a 0-10 visual analogue rating scale of pain intensity and a list of 15 pain descriptors to capture pain quality.

The Short Form Health Survey (SF-36) Questionnaire (Ware et al., 1993) is a self-report measure of subjective health status comprising 36 items across eight dimensions: physical function, social function, role limitations due to emotional problems, role limitations due to physical problems, mental health, energy/vitality, pain and general health perception.

The EQ-5D-3L (The EuroQoL Group 1990) descriptive system contains five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. It is applicable to a wide range of health conditions and treatments, and can provide an index value for health status.

The Acceptance and Action Questionnaire II (AAQ-II) (Bond et al., 2011) is a self-report measure of 10 items and was used in the present study to assess patients' ability to accept unwanted emotional experiences or thoughts arising from their experience of pain. It is suitable for use with chronic pain patients, and prior findings suggest greater acceptance leads these patients to function better and to suffer less (McCracken and Zhao - O'Brien 2010).

Where translations of study documentation from English were required (e.g. the patient information sheet, some outcome measures) these were provided by individual study centres for their respective country: Danish (Denmark); French (Canada – Quebec); German (Germany – Mainz and Erlangen, Switzerland); Polish (Poland) and Dutch (the Netherlands). This process was followed in reverse to translate qualitative study data into English. The translation process followed an iterative forward and backward approach with two translators, who were both fluent in the relevant two languages (one was the local study investigator and the other was independent from the study) to ensure consistency of meaning across countries. This followed a tried and tested validated process as previously used successfully by study collaborators (FB, RP, JM) (Heitz et al., 2010). Validation of new language versions of the outcome measures was conducted concurrently with this study.

2.5. Data Analysis

Quantitative and qualitative data were anonymised in each participating site, translated into English where required (as described above), and entered into a bespoke Microsoft Excel study template. These anonymised data were then sent electronically to the lead (UK) centre. Whilst we had asked participants to state whether they were non-recovered, partially recovered or fully recovered (as study consortium members felt only offering dichotomous recovered/non-recovered response options might be uncomfortable for some patients), for the purposes of study data analyses, partially-recovered and non-recovered data were combined under the category “non-recovered”. Similarly, as the treatment for CRPS 1 and 2 is the same according to IASP criteria and the challenges around definitions of recovery are the same, we did not differentiate between type 1 and type 2 in our analysis.

2.5.1. Quantitative Data

Data were analysed to identify frequency of recovery/non-recovery, gender, age, duration and location of CRPS and whether CRPS onset was spontaneous or followed trauma (e.g. fracture). The frequency of individual symptom reporting by recovery/non-recovery was also identified. Chi-squared tests of association were used to detect associations between the number of reported symptoms and self-reported recovery, and between recovery and demographic characteristics. Data from the non-recovered sub-sample were further examined with Odds Ratio analyses and Welch's t-tests to determine associations between symptoms and the limb that was affected (upper or lower - data from patients with CRPS in *both* upper and lower limbs were excluded from these analyses). The study was explorative in nature, hence no hypotheses of differences, or comparisons of data, between each country were made.

To analyse the Round 2 data, statements selected and ranked by participants were weighted for importance (priority 1=100%, 10=10%) and cumulative weighted percentages calculated for those statements quoted by $\geq 5\%$ of respondents, in order to identify the top 5 statements overall. Sub-group analyses identified the top three statements by geographical region, gender, recovery status (recovered/non-recovered), age, employment, duration and site of CRPS.

2.5.2. Qualitative Data

Training in thematic analysis was provided by FB and RP for a core analysis team of Expert Patient and academic researchers (IT, CS, YH, FB & RP). On receipt of completed questionnaires, Round 1 data were entered on to a common electronic template and transferred electronically to a single site (at the RNHRD, Bath UK). YH conducted an initial analysis of early responses using deductive analysis with QSR NVivo in order to identify the emerging themes (Braun and Clarke 2006). These themes were then categorised according to the World Health Organisation's (WHO) International Classification of Functioning, Disability and Health (ICF) (World Health Organization 2001) framework. The core analysis team and other members of the Consortium (selected based on their previous experience/knowledge of content analysis and to ensure representation across the participating countries), also jointly analysed a sample of data to ensure consistency of coding and subsequent categorisation according to this framework.

YH subsequently completed the data coding, analysing the data from non-recovered participants separately from that received from recovered participants, and consulting with the core analysis team for guidance where required. The core analysis team members reached consensus about any phrases not immediately fitting the classification system and where several different terms were judged by the researchers to describe the same issue, these were grouped together to form a universal description (Hasson et al., 2000). Editing of the original phrases and words was otherwise kept to an absolute minimum. Descriptions and grouping systems were also verified by two other members of the research team and by two other Expert Patient Researchers to confirm inter-rater reliability.

The frequency of themes within the data was noted for both the recovered and non-recovered subgroups and the top 50% of themes extracted. Led by JM, the Consortium members considered the statements for each of these themes that were felt to best represent patients' perceptions of recovery. The final agreed items were listed in a random order to form the questionnaire for Round 2.

3. RESULTS

3.1 Qualitative data

Round 1 questionnaires were sent to 679 patients and were returned by 347 (51%, 80% female, 91% non-recovered, 53% disease duration ≥ 3 yrs, mean age 53 years (range 18-85)) (See Table 1).

[Insert Table 1 here]

Dominant themes from the open text responses to the qualitative question about patient-defined recovery were as presented in Table 2. When these themes were categorised under the main WHO ICF framework, the majority of data fell into four key headings: activities of daily living; bodily functions and structures (including symptoms and pain); external factors (including medication use) and participation (e.g. housework, shopping). Personal factors (anxiety, depression) were least represented. Please see Table S1 for illustrative quotes from the most frequent themes, showing how these were categorised within the ICF framework, and indicating the country of origin of each quoted participant.

[Insert Table 2 here]

From the analysis of the Round 1 data, 62 statements were identified to represent the dominant themes of patient-defined recovery (See Table 3). These formed the basis of the Round 2 questionnaire, which was sent to the same 347 patients who had responded in Round 1.

[Insert Table 3 here]

3.2 Quantitative data

Of the 347 Round 1 participants, 310 reported their recovery status and completed symptom and standardised health outcome questionnaires: 280 (90.3%) “non-recovered”; 80% female; average age 52 years (range 19-85 years); 51% disease duration ≥ 3 years. Responses to other demographic questions showed: 70/40% upper/lower limb affected (some having CRPS in both an upper and lower limb); 55/53% right/left side affected (some having bilateral CRPS); 91/9% trauma-precipitated / spontaneous onset of CRPS. Responses to the standardised health outcome questionnaires are presented in Figure S3.

Both “non-recovered” and “recovered” participants reported symptoms in the prior 48 hours (see Table 4). The three most frequently reported symptoms for “non-recovered participants” were: muscle weakness (90%); a decreased range of motion in the affected limb (87%); and temperature differences from side to side (78%). This was also true for participants who classified themselves as “recovered”: 31% reported muscle weakness; 33% a decreased range of motion; and 27% temperature differences.

[Insert Table 4 here]

Self-reported recovery and number of symptoms were strongly associated ($\chi^2 = 124.94$, $df = 15$, $p < .001$). For those reporting < 5 symptoms, 34% reported themselves as recovered, compared to 2% of

those with 5 or more symptoms. There were no associations between self-reported recovery status and gender, disease duration, whether onset was post trauma or spontaneous, or limb affected.

Non-recovered participants with lower-limb CRPS more frequently reported allodynia (OR 1.93, CI = 1.12 – 3.33, $p = .021$), hyperalgesia (OR 2.60, CI = 1.40 – 4.83, $p = .003$), changes in hair growth (OR 1.86, CI = 1.08 – 3.21, $p = .035$), and involuntary muscle movements (OR 1.78, CI = 1.05 – 3.04, $p = .042$) than those with upper-limb CRPS. They also had poorer MPQ ($p < .01$), EQ-5D ($p < .05$), SF-36 Physical Functioning ($p < .001$) and Energy/Fatigue ($p < .05$) scores (see Table 5).

[Insert Table 5 here]

Round 2 responses, whereby patients ranked the relevance of the 62 statements, were received from 252 patients (73%, 77% female, 90% non-recovered) (see Table 6). The statements ranked as the top five priorities across the whole sample were: no longer having 1) CRPS-related pain, 2) generalised pain and discomfort, 3) restricted range of movement, 4) need for medication, and 5) stiffness in the affected limb/s. These themes were mirrored in the top three statements for each geographical region, apart from: having improved sleep and rest (UK, Denmark), and no longer having involuntary movement in the affected limb/s (The Netherlands).

The top three statements of most subgroups (males, females, recovered, non-recovered, age groups 30-50 and 50+, paid employment, non-employed, all disease durations, upper and lower limb CRPS) were all within the overall top five priority list. Individual exceptions were: having a better QoL (participants aged 18-30) and improved sleep and rest (non-paid workers).

[Insert Table 6 Here]

4. DISCUSSION

While it is known that CRPS can resolve spontaneously, studies suggest that for some patients, symptoms can persist and lead to long term-disability (Bean et al. 2016; Beerthuizen et al. 2012; De Mos et al. 2009). The primary aim of this international study was to define recovery from the patients' perspective, and to understand the factors that may influence this.

When each participant was asked to describe what would lead them to consider themselves recovered from CRPS, responses showed, that patient-reported impacts of CRPS fall across the breadth of the WHO ICF categories. The largest number of reports related to: activities of daily living; bodily functions and structures (including symptoms and pain); external factors (including medication use), and participation (e.g. housework, shopping). These findings support prior studies suggesting CRPS interferes with many aspects of life including self-care, work and mobility (Kemler and de Vet 2000; Sharma et al., 2009).

Interestingly, psychological factors, such as anxiety and depression, which fall within the ICF “personal factors” category, were least represented amongst the themes patients reported as important for recovery. The literature on the role of psychological factors in CRPS is contradictory. While some studies suggest psychological factors have little bearing on the development and longevity of CRPS (Beerthuis et al. 2009; Beerthuis et al. 2011; Puchalski and Zyluk 2005), others have found associations between CRPS outcomes and anxiety (Bean et al. 2015; Bean et al. 2014b; Dilek et al. 2012). In our study, patient research partners within the research team, suggested affect is a consequence of CRPS symptoms, not a symptom per se. Previous research has similarly concluded altered psychological functioning is a natural outcome of chronic pain, rather than a specific psychological profile characteristic of CRPS patients, (Lohnberg and Altmaier 2013). Furthermore, the phrasing of our open question may have elicited patients’ *primary* complaints, such as pain and function, rather than secondary consequences of these symptoms, such as psychological distress.

Through selection and ranking of the *most* important factors that would enable participants to personally consider themselves recovered, participants reported they want, in priority order: to be relieved of CRPS pain, and generalised pain and discomfort; to have improved movement; and to have a reduction in medication, and stiffness in their limbs.

Given the intensity of CRPS pain, we were not surprised that this was patients’ highest priority. However, the frequency with which the factor: “generalised pain and discomfort” was identified by all sub-groups, was unanticipated. Widespread muscle hyperalgesia affecting non-CRPS affected limbs and the cheek area, has previously been reported in CRPS patients with longstanding disease (van Rooijen et al., 2013). It is considered most likely this unspecific pain relates to central sensitization, a process in which innocuous stimuli become, and remain painful in chronic pain conditions, such as CRPS (Goebel 2011). Our findings underline the importance of using measures to capture non-specific, as well as distinct, CRPS pain in research and clinical practice, and to consider both aspects when determining therapeutic interventions.

A recent qualitative study, exploring what patients consider important to recovery following hip fracture, found mobility, and its relevance to personal care and valued day-to-day activities, was the most important factor (Griffiths et al., 2015). Our data similarly suggest that while reduction of pain remains a fundamental treatment aim, the patients’ desire for restoration of function supports multidisciplinary treatment approaches focussing on the goals and needs of daily living.

We are not aware of previous studies that have specifically identified the importance of reducing reliance on medication, when defining recovery in musculoskeletal conditions. Whilst medication may be one cornerstone for the treatment of chronic pain, our data suggests that people with CRPS may value exploring non-pharmacological coping and treatment strategies in order to meet their goal of

reducing medication. Cognitive behavioural approaches, such as Acceptance and Commitment Therapy (Hayes et al., 2006), may be helpful in this regard.

There is a paucity of research into individual differences in the impacts of CRPS. However, our data suggest that treatment targets vary little between patients; indicating group based therapeutic interventions maybe as effective as more individually tailored treatment approaches. We were particularly interested in the consistency of factors identified by participants as most important in defining recovery across the subgroups. Results showed that these factors were mostly irrespective of gender, recovery status, age, employment status, disease duration and site of CRPS (upper or lower limb). The minor country-specific differences we saw could be attributable to referral variation. For example, CRPS clinicians in The Netherlands have particular expertise in CRPS-related movement disorders and this may explain why resolution of involuntary movements was a particular priority for the Netherlands cohort.

Muscle weakness and decreased range of motion were the most frequent symptoms reported by participants in our quantitative data. These findings correspond to the importance of improved motor function and reduced stiffness, as identified as recovery priorities in our qualitative data, and underline the importance of addressing factors affecting physical function in CRPS treatment pathways. While temperature differences between the affected and unaffected limb were also frequently reported symptoms, our findings suggest autonomic features are considered by patients to be less important in their definition of recovery than aspects of their condition that deleteriously impact daily activities.

Interestingly pain was not among the most frequently reported symptoms, despite it being identified as of highest importance to recovery. It is possible that these, seemingly contradictory findings may be the product of response shift (Schwartz et al. 2007), and the nature of the dichotomous questions asked. In our study, patients were asked whether or not, in the last 48 hours, they had experienced “pain going on *longer than expected/greater than expected*” and whether stimuli that “*normally* do not cause pain”, or “*normally* cause only slight pain” had been painful/more painful. It is plausible that participants’ acceptance of their everyday pain meant they only reported pain *beyond* that which was typical for them, and which they already considered as “normal”.

Given the nature of CRPS, and the breadth of symptoms in diagnostic criteria, it is unsurprising our data showed, that the likelihood of a participant considering him/herself to be recovered was closely related to the number of symptoms reported. However, even those who classified themselves as “recovered”, had still experienced symptoms in the prior 48 hours. In a similar way, post myocardial infarction, patients have also reported recovery as an ongoing and unstable process of learning to live with feeling “different” from before (Tod 2008). This presents an interesting insight into how people conceptualise recovery and suggests that it is more complex than the simple absence or presence of symptoms. Within this context, it poses the question what constitutes appropriate treatment to address the residual functional needs people with CRPS. For example, should people who no longer

meet the diagnostic criteria, but who nevertheless have ongoing disabling symptoms, still be offered the full breadth of “usual” CRPS care, or should they receive more specific approaches, individually tailored to their remaining functional impairments? Future studies are needed to determine the most functionally beneficial and cost effective solutions across the disease trajectory.

Sub-group analysis of our quantitative data from non-recovered patients, indicated poorer outcomes for those with lower limb CRPS, than those with CRPS of the upper limb. This was true for our standardized measures of pain, physical functioning, QoL and energy/fatigue. These findings fit well with previous work citing lower self-reported QoL in the physical domain of the SF-36, for those with lower limb CRPS (van Velzen et al., 2014).

A contributing factor to these poorer outcomes in lower limb CRPS may be our finding that these participants had a higher mean pain score on the MPQ, and more frequently reported allodynia and hyperalgesia, than those with upper limb CRPS. Furthermore, they more frequently reported changes in hair growth and involuntary muscle movement. Involuntary movements have been previously reported to occur significantly more often in CRPS affected legs than arms (Frettlöh et al., 2006). Beyond the respective prevalence of upper and lower limb CRPS, we are not aware of any other studies that have compared and contrasted the incidence and specificity of symptoms according to localization. More research is needed to understand the differential implications of CRPS site, on patient outcomes.

A limitation of our study was the small "recovered" sample (9%). This sample was probably a consequence of our pragmatic recruitment strategy, approaching participants from CRPS databases and research lists. The greater duration of CRPS, the more likely a patient would be enrolled into a condition-specific database. Furthermore, those who are fully recovered may be less inclined to complete a CRPS-focused questionnaire, as it lacks relevance to them any more. A lack of statistical power in the available sample size therefore precluded analysis of between group differences.

We are mindful that our study was reliant on self-report of symptoms, which were not clinically verified and that this may be considered a study limitation. Furthermore, much of the outcome measure data was unique to the study protocol and therefore only available for those who completed and returned the questionnaires. For this reason, and because clinical records differ greatly between countries, we were unable to investigate any potentially significant differences between those who did, and did not return questionnaires. Future studies with greater equipoise between recovered/non-recovered cohorts, the inclusion of a clinical assessment, and consideration of study participant/non-participant data would be informative.

Our data adds a unique perspective to current understanding of recovery, as defined by patients. Our findings suggest a very small number of themes are of highest importance to people with CRPS in their definition of recovery, and these vary little with demographics. Irrespective of where a person

with CRPS is in the disease trajectory, and whether or not they still meet diagnostic criteria, they want their CRPS-related pain, generalised pain, movement difficulties, and medication reliance to be addressed, above all other factors, for them to consider themselves recovered. These factors should therefore be considered as foremost in the development and design of future treatments and multidisciplinary rehabilitation programmes.

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Author contributions

As members of the international consortium convened for this study, all authors made substantial contributions to either the study design and methodology, data acquisition or data analysis and interpretation. All authors discussed the study findings, have been consulted in the drafting of the final article, and have given their approval for publication. Dr Llewellyn and Professor McCabe contributed equally to this work and are joint first authors.

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Patient Characteristics	N	%
Gender		
Male	68	19.7
Female	277	80.3
Mean age (SD) (Range)	53 (12.91) (18-85)	
Employment status		
Employed/self employed	92	27.0
Employed part time	41	12.0
Housewife/husband	27	7.9
Unemployed	21	6.2
Voluntary worker	2	0.6
Retired	79	23.2
Ill-health retired	59	17.3
Student	8	2.4
Other	12	3.5
Mean years in education from age 6 (SD) (Range)	18 (21.35) (3-25)	
Site of CRPS [†]		
Upper right limb	138	39.8
Upper left limb	119	34.3
Lower right limb	80	23.1
Lower left limb	85	24.5
Dominant hand		
Right	303	88.3
Left	40	11.7
Disease duration		
Less than 1 yr	42	12.3
1-3 years	120	35.1
≥ 3 years	180	52.6
Self-reported recovery		
Recovered	33	9.5
Non-recovered	314	90.5

[†] Some participants had CRPS in more than one limb, hence summing these figures will give a total which exceeds the overall sample size (N=347 / 100%).

Table 1. Demographic characteristics of Round 1 sample.

Canada	Denmark	Germany	Netherlands	Poland	UK	USA	Switzerland
Pain Sensations	Pain Sensations	Pain Sensations	Pain Sensations	Muscle and Movement Functions	Pain Sensations	Pain Sensations	CRPS Symptoms
Medical Services	CRPS Symptoms	Muscle and Movement Functions	Mobility	Pain Sensations	CRPS Symptoms	Recreation and Leisure	Pain Sensations
CRPS Symptoms	Mobility	CRPS Symptoms	CRPS Symptoms	CRPS Symptoms	Mobility	CRPS Symptoms	Mobility
Domestic Life	Sleep Functions	Mobility	Domestic Life	Mobility	Recreation and Leisure	Muscle and Movement Functions	Recreation and Leisure
Recreation and Leisure	Work and Employment	Psychological Factors	Muscle and Movement Functions	Medical Services	Muscle and Movement Functions	Self Care	Muscle and Movement Functions
Mobility	Muscle and Movement Functions	Sleep Functions	Recreation and Leisure	Self Care	Self Care	Functioning as Normal	Sleep Functions
Muscle and Movement Functions	Recreation and Leisure	Medical Services		Carrying Out Daily Routine	Domestic Life	Reproductive Functions	Self Care
Sleep Functions	Restlessness	Usage of Computer & Writing		Domestic Life	Carrying Out Daily Routine	Medical Services	Medical Services
Self Care	Medical Services	Functioning as Normal		Sleep Functions	Medical Services	Work and Employment	Work and Employment
Psychological Factors	Self Care			Work and Employment	Work and Employment	CRPS Ruling Life	Domestic Life
	Life Before CRPS				Psychological Factors	Psychological Factors	Psychological Factors

Table 2. Top 50% of themes in rank order from Round 1 data by participating country

1.	If I did not have involuntary movement (incl. tremor) and cramps in my affected limb/s
2.	If I could go shopping
3.	If I did not suffer from temperature changes in my affected limb/s
4.	If I did not have increased muscle tension in my affected limb/s
5.	If I was not restless
6.	If I did not have colour changes in my affected limb/s
7.	If I could use stairs
8.	If the appearance of my limb/s was/were normal
9.	If I could generally have more confidence
10.	If I was not depressed
11.	If I was less tired
12.	If I could feel good inside
13.	If I could take part in indoor activities – hobbies
14.	If I did not need medication
15.	If I was able to prepare my hair and nails
16.	If I did not have feelings of negativity
17.	If I did not have fear / worries
18.	If I had a better quality of life
19.	If I could drive a vehicle
20.	If I did not need the use of medical aids (e.g. crutches)
21.	If I could wash clothes
22.	If I did not have skin changes in my affected limb/s
23.	If I could wear the clothing and jewellery of my choice
24.	If I could feel acceptance of CRPS
25.	If I did not have CRPS related pain in my limb/s anymore
26.	If I did not have hair and nail changes in my affected limb/s
27.	If I could live independently
28.	If I could return to work and employment
29.	If I did not have stiffness in my affected limb/s
30.	If I could stop feeling useless
31.	If I could eat (normally)
32.	If I could travel more
33.	If I could walk
34.	If I did not have generalised pain and discomfort
35.	If I could carry out my daily routine
36.	If I could feel in control
37.	If I could stand
38.	If I was not affected by sweating in my affected limbs
39.	If I could do housework
40.	If I could wash and toilet independently
41.	If I had more stamina
42.	If I could prepare meals
43.	If I did not have internal agitation
44.	If I could take part in family activities
45.	If I could carry, handle and move objects
46.	If I did not have headaches
47.	If I did not have limb swelling
48.	If my sleep & rest improved
49.	If I did not have muscle weakness in my affected limbs
50.	If I did not feel stress
51.	If my limb felt it belonged to me
52.	If I could write better
53.	If I could receive the right medical treatment
54.	If I could feel at ease
55.	If I could dress myself
56.	If I could take part in more sports and exercise
57.	If I could have a clear mind
58.	If I could use a computer
59.	If I did not have mood swings
60.	If I could take part in a social life
61.	If I did not have restricted range of movement in my affected limb/s
62.	If I could take part in outdoor activities/hobbies
63.	I do not find any of these statements important with regards to my recovery from CRPS.

Table 3. Statements representing patients' definitions of recover, derived from Round 1 data.

% Yes response to:	Responses to Recovered / Non-Recovered question (N=310)	
	Non-recovered <i>n</i> =280	Recovered <i>n</i> =30
Pain going on longer than expected, pain greater than expected.	63.4	17.9
Stimuli that normally do not cause pain are painful now.	57.8	13.8
Stimuli that normally only causes slight pain are now painful	67.9	17.2
Temperature differences from side to side	78.1	26.9
Colour differences from side to side	63.1	16.7
Sweating differences from side to side	51.3	10.3
Swelling (oedema) of affected limb	70.7	23.3
Changes to the growth of your nails on affected part	45.3	16.7
Changes to the growth of hair on affected part	37.5	13.3
Changes to the appearance of your skin on affected part	69.1	20.0
Muscle weakness in affected limb	89.9	31.0
Involuntary muscle tremors, or shaking	55.1	6.7
Sustained muscle contractions resulting in involuntary positioning of limb	46.5	10.0
Decreased range of motion in affected limb	87.0	33.3
Involuntary muscle movements.	47.8	13.3

Table 4. Percentage reporting specific symptoms by self-reported recovery status

Measure	Non-Recovered participants with CRPS in:						<i>t</i>	<i>p</i>	D
	Lower limb only			Upper limb only					
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD			
AAQ	76	46.99	13.69	159	48.29	11.87	0.71	.478	0.105
MPQ	81	25.08	11.37	140	20.86	11.48	2.65	.009	0.371
EQ5D	78	0.39	0.36	162	0.51	0.34	2.42	.017	0.341
SF-36									
Physical Functioning	84	40.11	27.48	165	62.81	22.70	6.52	<.001	0.934
Physical Health	84	18.15	31.61	165	25.30	37.35	1.59	.115	0.202
Emotional Problems	83	38.55	42.76	165	44.65	45.16	1.04	.300	0.134
Energy/Fatigue	84	36.17	22.92	166	43.96	21.22	2.60	.010	0.358
Emotional Well-being	84	53.22	22.20	166	57.41	22.24	1.41	.161	0.189
Social Functioning	84	49.85	26.57	166	56.85	29.31	1.90	.059	0.247
Pain	84	34.38	23.30	166	38.42	26.65	1.23	.219	0.159
General Health	83	46.93	23.70	166	47.35	23.05	0.13	.894	0.018

Table 5. Mean measures by lower limb only and upper limb only (*t* denotes absolute *t*-value in Welch's *t*-test; *p* the corresponding *p*-value, and *d* denotes the sample estimate of Cohen's *d*).

Overall top five statements, N=252																							
Statement number		Weighted % score																					
25		51.03																					
34		28.19																					
61		22.93																					
14		20.39																					
29		15.46																					
		If I did not have CRPS related pain in my limb/s any more																					
		If I did not have generalised pain and discomfort																					
		If I did not have restricted range of movement in my affected limb/s																					
		If I did not need medication																					
		If I did not have stiffness in my affected limb/s																					
Sub groups		Geographical area [†]							Gender		Recovery Status		Age			Duration of CRPS			Employment status			Limb affected ^{††}	
Top three recovery statements 1 = first priority 2 = second priority 3 = third priority		North America	Germany	Poland	The Netherlands	Switzerland	Denmark	UK	Males	Females	Non-recovered	Recovered	Age 18-30	Age 31-50	Age 51+	<1 year	1-3 years	>3 years	Paid employment	Non-paid work	Not employed	Upper	Lower
<i>Top 5 statements overall</i>	n=	53	54	35	23	35	21	31	49	161	189	21	11	63	130	28	68	116	71	21	111	169	90
	If I did not have CRPS related pain in my limb/s any more	1			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	If I did not have generalised pain and discomfort	3	3	2		2	2		3	2	2	2	2	3	3		2	3	2		2	3	3
	If I did not have restricted range of movement in my affected limb/s		1	3	2	3				3		3			2	2			3	3	3	2	
	If I did not need medication	2	2					3	2		3			2			3	2					2
	If I did not have stiffness in my affected limb/s			1												3							
	If my sleep and rest improved						3	2											2				
	If I did not have involuntary movement (incl. tremor) and cramps in my affected limb/s				3								3										
	If I had a better quality of life																						

[†] Individual participants were not identifiable from Swiss Round 2 data and are therefore not included in other demographic sub-group totals.

^{††} Some participants had CRPS in both an upper and lower limb.

Table 6. Statements identified by participants as most important to their definition of recovery from CRPS

