A Delphi Study to Define Core Clinical Outcomes for Inclusion in a Complex Regional Pain Syndrome International Research Registry and Data Bank

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Abstract

Complex Regional Pain Syndrome (CRPS) clinical trials have historically captured a diverse range of outcomes. A minimum set of CRPS patient-reported outcomes has been agreed for inclusion in a future CRPS international clinical research registry and data bank. This current study aimed to identify a complementary set of core clinical outcomes. Clinicians and researchers from the international CRPS community informed the content of a 2-round electronic Delphi study. Participation was invited from members of the International Association for the Study of Pain CRPS special interest group and the International Research Consortium for CRPS. In Round 1, participants rated the relevance of 59 clinical outcomes in relation to the question "What is the clinical presentation and course of CRPS, and what factors influence it?" (1=not relevant, 9=highly relevant). In Round 2, participants re-rated each outcome in the light of Round 1 median scores. The criterion for consensus was: median score ≥7, agreed by 75% of respondents. The core study team considered the feasibility of data collection of each identified outcome in agreeing final selections. Sixty respondents completed both survey rounds, with responses broadly consistent across professions. Nine outcomes met the consensus criterion. Final outcomes recommended for inclusion in the core clinical set were: record of medications, presence of Post-Traumatic Stress Disorder, extent of allodynia, and skin temperature difference between limbs. Study findings provide robust recommendations for core clinical outcome data fields in the future CPRS international clinical research registry. Alongside patient-reported outcomes, these data will enable a better understanding of CRPS.

Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition usually affecting a single limb, which manifests in sensory, motor, trophic and autonomic abnormalities. In recent years, revised diagnostic criteria have improved standardisation across research study participants [19]. The multidimensional nature of CRPS means clinical trials currently use a diverse range of outcome measures [15], thus making it difficult to synthesise data across sites. Furthermore, CRPS is categorised as an 'orphan disease' (incidence rates from 5.46 to 26.2 per 100,000 person years [22,27]). Low incidence rates and non-standard assessment protocols have limited the ability to conduct large, global CRPS studies [6] required to inform evidence-based treatment guidelines and provide mechanistic and clinical knowledge for the development of targeted therapies [5].

To address these limitations, an international consortium was established in 2013, under the auspices of the International Association for the Study of Pain (IASP) CRPS Special Interest Group (SIG). The Core Outcome Measures for complex regional PAin syndrome Clinical Trials consortium (referred to hereafter as the COMPACT consortium) comprises patients, clinicians, researchers and industry representatives from twenty countries across 6 continents.

COMPACT set out to identify a minimum core set of outcome measures advocated for use in all future CRPS clinical studies, with the ultimate aim of creating the first international clinical research registry and data bank for CRPS.

A core outcome measurement set can be defined as an agreed, standardised set of outcomes, which should be measured and reported in all clinical studies in a particular condition [30]. These have been increasingly developed in response to the inconsistency of outcome measures used in clinical trials investigating the same disease or condition [4,14]. Previous initiatives have advocated the use of core outcome measurement sets in pain (Initiative on Methods Measurement and Pain Assessment in Clinical Trials; IMMPACT [12]) and rheumatology clinical trials (Outcome Measures in Rheumatology; OMERACT [13]). This work provided a starting point for the COMPACT collaboration, due to a degree of overlap between these disorders and CRPS – a chronic pain condition that impacts limb function.

In 2017 the COMPACT consortium recommended a core set of patient-reported outcome measures as the basis for the data fields in a future international registry and data bank [16]. Concurrently, the consortium initiated preparatory discussions to define an additional, and complementary, minimum core set of *clinical* outcomes.

It is intended that a future registry containing both data sets will enable us to answer the overarching research question "What is the clinical presentation and course of CRPS, and

what factors influence it?" and to provide a springboard for further studies using a novel, large and consistent set of CRPS outcomes and demographic data.

The current study therefore sought to: 1) explore the potentially relevant clinical outcomes for inclusion in the future registry; 2) identify the minimum number of CRPS clinical outcomes that together will best address the COMPACT consortium's stated overarching research question; and 3) make recommendations for the effective and efficient collection of these core outcome items, internationally.

Methods

Ethical approval and funding

Ethical approval was received from the Research Ethics Committee of the Faculty of Health and Applied Sciences at the University of the West of England (HAS.19.02.142). Funding was gratefully received from the Reflex Sympathetic Dystrophy Syndrome Association.

Development of the study protocol

There was recognition from the outset of the importance of ensuring a multi-disciplinary perspective for this project. The existing COMPACT consortium, International Research Consortium for CRPS (IRC) and the International Association for the Study of Pain (IASP) CRPS Special Interest Group (SIG), all have multi-disciplinary membership. Patient and industry representatives are also key members of COMPACT. At an international COMPACT meeting in Mainz, Germany, also attended by invited clinical academics whose areas of expertise are not directly focused on CRPS, but are closely aligned to it, the COMPACT consortium held preliminary discussions. Attendees agreed on the study protocol for an electronic Delphi (e-Delphi)[2] survey methodology to achieve consensus amongst clinicians, academics and researchers working in the field of CRPS in identifying the clinical outcomes for potential inclusion in the COMPACT core outcome set.

The Delphi technique comprises a series of sequential questionnaires (usually 2-3), which are interspersed by controlled feedback that seeks to combine opinion into a group consensus [21]. Consensus methods are useful for situations where there is incomplete knowledge or a requirement to set an agreed set of priorities [10,21]. As there were no published data on the minimum core set of clinical outcomes for CRPS, this was considered an appropriate technique to use to explore this topic and to set a priority list. A particular strength of a consensus approach is that each participant has an equal say so that no one voice is dominant [21]. The Delphi Technique had been used successfully before by

members of the research team to answer other questions in relation to the care and treatment of those with CRPS [8,20].

In the Summer of 2018, a systematic literature search was conducted to identify outcome measures used in CRPS prospective and retrospective cohort and observational studies, pilot and feasibility studies, and randomised controlled trials from 2000 (Embase, Medline, CINAHL Plus, AMED, PsychINFO, 2000-2018, human, adult) and 2451 relevant articles were identified. Following screening, 125 articles were retained, from which individual clinical outcomes reported could be extracted and summarised e.g. measures of activity, measures of allodynia, measure of grip strength; psychological measures. (The screening process is given in Figure 1.) In extracting the outcomes reported in the final articles, signs and symptoms from the Budapest diagnostic criteria for CRPS [19] were excluded when these were presented in studies in a checklist format, or used in the study for diagnosis purposes only. Quantitative objective signs were included when measured individually within the research design. This process identified 44 potential clinical outcome categories for consideration for inclusion in the e-Delphi survey.

The 44 outcome categories were presented to 27 physicians, therapists, and researchers from across the CRPS community at a workshop in Boston, USA in September 2018. Workshop attendees were asked to review the list, to provide comment if clarification or detail were needed, to add any missing items, and to offer suggestions for further refinement. Working in groups, feedback was collected in writing and via discussion. The workshop attendees agreed respondents would rate each potential clinical outcome on a scale of 1-9 (1 = not relevant and 9 = highly relevant) in terms of its relevance to the overarching COMPACT research question of "What is the clinical presentation and course of CRPS, and what factors influence it?" Consensus would be considered achieved for any outcome item with a median group rating of ≥7 [21], and which had been rated as ≥7 by ≥75% of respondents.

Informed by the workshop and by individual consultations with clinicians and measurement scientists, the list of 44 outcome categories was subsequently refined in more detail by the study team. Twenty-seven of the original categories were retained or redefined as specific outcome items. Of the other 17 categories, five were removed because they were determined to be out of scope as potential minimum core dataset items. Twelve further categories were considered sufficiently captured within the already selected outcome items, or were removed in response to feedback indicating they required greater specificity in their definition (see Table 1). For example, the motor function category was removed as an item in its own right, but a range of specific items relating to motor function were added to the physical function category, such as sit-to-stand test performance. Similarly, sympathetic skin response was removed as other sudomotor and vasomotor items were already included in the agreed outcome items list.

From these discussions, 32 new/more specific items were also added, giving a final total of 59 items presented across ten broad categories: body schema/body image, co-morbidities, family history, pain & other sensory perceptions, physical function, physiological, medications, psychological, trophic changes, and vasomotor dysfunction. Individual items in each category are given in Table 2.

The e-Delphi survey was designed for administration of both rounds via the Qualtrics Insight survey platform. Participants could access the survey via a PC or mobile device.

Study participants

Delphi surveys can range from quite small sample sizes (n=15-50) up to much larger samples (n>300) [21]. The study protocol had specified that participants in the e-Delphi survey should be drawn from the memberships of the IASP CRPS SIG (n= approx. 270) and the IRC (n= approx. 70). Acknowledging that there would be some overlap in membership, the total potential sample was therefore anticipated to be above a desirable minimum of 50.

In April 2019, potential e-Delphi survey participants were contacted via a personal email invitation sent by the IASP SIG for CRPS and the IRC to the members of their respective organisations. The email invitation included an overview of the study, with a link to access further information and the first round of the e-Delphi survey. This invitation was circulated again two weeks after the first email, in an attempt to optimise recruitment.

Procedure

E-Delphi Round 1
On accessing the Round 1 survey, potential participants were reminded of the study aims and why they had been invited to take part. A private YouTube link to a video-scribe outlining the study context and process was provided. The video-scribe included an explanation of the sequential process of the study and the aims of each round of questionnaires. A full participant information sheet was also provided via an embedded link on the first page of the electronic survey, and before the respondent was asked to decide whether to participate. Providing this type of information to potential participants has been shown to increase commitment to the study and improve response rates in subsequent rounds [9,29].

Consent to participate in the study was received when the respondent confirmed their wish to take part. Clicking this option gave them access to the Round 1 survey questions. Respondents who subsequently stated a decision not to participate (n=1) were thanked and the link closed.

Participants who continued to the Round 1 survey were asked to provide their email address so they could be contacted directly, without the need to go back through the IASP SIG or IRC, for the conduct of the subsequent round.

Prior to viewing the Round 1 survey questions, participants were reminded of the overarching COMPACT research question: "What is the clinical presentation and course of CRPS, and what factors influence it?" They were then asked to review the list of 59 clinical outcomes and to rate the relevance of each outcome to the research question on a 9-point Likert scale where 1=not relevant and 9=highly relevant. The survey included space beneath each response for free text to be added so participants could justify their selected response or add a comment. The responses to Round 1 were collated so as to create Round 2.

E-Delphi Round 2

Those respondents who completed Round 1 were presented with an individualised questionnaire. This comprised the full list of outcomes from Round 1 showing their individual score of relevance for each outcome and the group median score for each outcome. Any comments added in Round 1 were also displayed in an anonymised manner. Participants were asked to consider all of this information and to re-rate each outcome. Figure 2 shows example screens from the survey as viewed on a PC and on a mobile device.

Post e-Delphi workshop

Results of the e-Delphi survey were presented to core members of the study team in a workshop held in Valencia, Spain in September 2019 for final selection of outcomes. Pragmatic considerations for each potential outcome included: the anticipated availability of standardised measurement equipment in normal clinical practice; time constraints during clinical consultations; and whether similar outcomes were already sufficiently captured within the Budapest diagnostic criteria, the CRPS Severity Score, or the patient-reported outcomes already incorporated within COMPACT [16]. Through this method, the team identified which outcomes should be included in the clinical core set, and which should be included within the clinical data set as 'optional for research purposes'. The final agreed 'core' and 'research optional' clinical outcomes were thereby defined, and recommendations for their measurement were subsequently discussed.

Data Analysis:

All data from Round 1 were exported from the e-Delphi survey tool (Qualtrics) and, via Microsoft Excel, the median score of each questionnaire outcome item was calculated to inform Round 2 [21]. Free text comments were assigned to their questionnaire item. Using Excel, the median score of each outcome item in Round 2 was calculated, as was the percentage of ≥7 responses for each item. Those outcome items with a final group median that met the consensus criterion, of a median a score of ≥ 7 as agreed by 75% of the study group [21], were identified. A sub-group analysis of Round 2 data identified outcome items rated as ≥7 by different professions.

Results

E-Delphi Round 1

Responses to the Round 1 survey were received from n=74 participants: 53% (n=39) clinical academic, 34% (n=25) clinician, 13% (n=10) academic (see Table 3).

Group median scores for individual outcome items in Round 1 ranged from 3.0 (hearing performance, visual performance, assessment of cardiac performance) to 8.5 (degree and extent of brush-evoked allodynia). The six outcome items that met the consensus criterion (median score ≥7 on 1-9 scale as rated by 75% of respondents) were: record of diagnosed psychological co-morbidities (8.0, 78.4%); degree and extent of brush-evoked allodynia (8.5, 87.8%); degree and extent of hyperalgesia (8.0, 87.8%); name and dosage of current medications (8.0, 78.4%); clinical assessment of anxiety (8.0, 77.0%); clinical assessment of depression (8.0, 79.7%) (See Table 4). Free-text comments were provided by 22 respondents, reinforcing the considered relevance/non-relevance of ratings.

E-Delphi Round 2

Responses to the Round 2 survey were received from n=60 (86%) of the earlier round participants: 53% (n=32) clinical academic, 30% (n=18) clinician, 17% (n=10) academic. Professions represented were broadly similar to Round 1: Physician 51% (n=31), Researcher 23% (n=14), Physiotherapist 15% (n=9), Surgeon 5% (n=3), Nurse 2% (n=1), Occupational Therapist 2% (n=1), Psychologist 2% (n=1). In terms of professional expertise, 62% (n=37) of respondents had been working in the field of CRPS for more than 10 years, 20% (n-12) for 6-10 years and 18% (n=11) for ≤5 years. Of those respondents working clinically in CRPS (n=50), the majority (58%, n=29) stated they see 0-5 cases per month, 22% (n=11) saw 6-10 cases per month and further 20% (n=10) saw 11 cases or more. The characteristics of Round 2 participants are given in Table 3.

Following the re-rating of items by Delphi participants in the light of the Round 1 median scores, nine items met the group median score consensus criterion in Round 2 (see Table 4). These were: record of diagnosed psychological co-morbidities (8.0, 86.7%); degree and extent of brush-evoked allodynia (8.0, 86.7%); degree and extent of hyperalgesia (8.0, 88.3%); level of activity (as determined by wearable devices) (8.0, 85.0%); name and dosage of current medications (8.0, 85.0%); clinical assessment of anxiety (8.0, 86.7%); clinical assessment of depression (8.0, 86.7%); clinical assessment of post-traumatic stress disorder (8.0, 86.7); and quantitative assessment of skin temperature (8.0, 78.3%). Individual item median group scores for all outcomes in Round 2 are given in Table 5.

Analysis by professional group indicated broad consistency of ratings amongst different professions. However, a larger percentage of Therapists/Psychologists/Nurses rated medications, allodynia, psychological comorbidities, PTSD and emotional outcomes as important, than did physicians/surgeons (see Figure 3). Beyond those items that met the overall consensus criteria, 83.3% of Therapists/Psychologists/Nurses also rated global body perception as ≥7, whilst a score of ≥7 for the range of movement item was received from 79% of Physicians/Surgeons. Additionally, 75% of Therapists/Psychologists/Nurses rated each of the trophic change items (hair, nails and skin) as ≥7.

Consensus workshop

All potential outcomes were assessed by the study team for feasibility and acceptability for use in clinical settings. The following outcomes were agreed upon for inclusion in a final core data set:

Name and dosage of current and previous medications

A variety of pharmacological treatment approaches are used in CRPS care, commonly including corticosteroids, anticonvulsants, and analgesic antidepressants [6]. Similarly, opioid analgesics and topical patch treatments and creams may be prescribed to provide pain control that allows for better engagement in normal daily activities [6]. Medications are commonly used in combination [18] for the relief of pain and are not considered curative treatments [23]. Given the widespread use of medications by people with CRPS, it was considered important to include in recommendations from the current study that a record of current medications (medications being taken at the time of first assessment) be captured, so that associations between pharmacological treatments and clinical signs might be detected. Where feasible, previous CRPS medications (at any time point) and other non-CRPS current medications will also be optionally recorded to provide further information about each patient's treatment journey.

Standardised measure of Post-Traumatic Stress Disorder (PTSD)

Psychological factors such as depression and anxiety are known to be associated with CRPS outcomes, such as disability and pain [5]. Furthermore, evidence suggests a higher prevalence of post-traumatic stress disorder (PTSD) in people with CRPS, compared to the general population, and it has been asserted to be a significant comorbidity of the condition [28]. However, a PTSD diagnosis is often not considered in pain services where the focus may be on physical symptoms and distress [1]. It was therefore considered important to include a screening assessment for PTSD within the COMPACT core set. Whilst structured clinical interviews can be used for diagnosis, short self-reported scales have been found to have similar accuracy and to be valid in chronic pain rehabilitation [1]. As clinical time is at a premium, it was therefore recommended that a brief patient-reported scale be added to the existing COMPACT patient-reported core outcome set. It was noted that, for completeness, the selected scale needs to include the symptoms as defined in the International Classification of Diseases 11th Revision – ICD11 [31] within its items. The assessment instrument chosen by the study team is the PTSD-8 [17]. This is an eight-item instrument with three subscales: intrusion, avoidance and hyperarousal, thereby covering the three DSM-IV PTSD symptom clusters [32]. Each item is rated on a four-point Likert scale (1= not at all, 4 = very often). The PTSD-8 has been shown to have good psychometric properties, and has been applied and validated in a variety of samples including chronic pain rehabilitation [1,17].

Allodynia

Allodynia is one diagnostic criterion for CRPS [19]. In CRPS research, allodynia is typically assessed using the repeated application of an innocuous stimulus, usually stroking with a brush, to identify the allodynic area. However, this method is considered difficult to standardise in terms of tools and techniques [24] as well as being time consuming (for example, it may require the patient to carefully remove garments on, or near to, the affected area). As the presence/absence of allodynia is already captured within COMPACT in the CSS, it was agreed that a useful clinical outcome would be to map the body areas corresponding to each patient's allodynia using a format similar to the Michigan Body Map [7]. This type of simple body map, where broad areas can be indicated for the presence of allodynia, was considered appropriate. However, recognising that this, in itself, could take time, it was agreed to recommend this as an optional COMPACT research clinical outcome.

Quantitative assessment of skin temperature

Skin temperature changes are characteristic of CRPS and temperature asymmetry between the CRPS-affected limb and the contralateral limb is included in the diagnostic criteria [19]. Whilst thermal imaging cameras have been determined to be accessible for use with patients with CRPS [11], and thermography is often used in clinical settings, assessments are difficult to standardise across research centres due to the variety and availability of equipment. It was considered that an alternative, low-cost and easier-to-administer

approach to assessing temperature differentials between limbs can be provided by the use of an infrared thermometer. Calibration of equipment between centres is not required as it is the *difference* between limb temperatures that is of interest, not the absolute temperatures of the limbs. Infrared thermometers have been recommended, particularly where an understanding of the severity of a patient's CRPS is sought [25]. Quantitative assessment of skin temperature using an infrared thermometer, and adhering to a standardised administration protocol was agreed for inclusion in COMPACT as "optional for research purposes".

Protocols for the measurement of the agreed core/optional clinical outcomes are in development and will be distributed to all research centres contributing data to the CRPS International Registry.

The rationales for the inclusion of the above and the exclusion of other items i.e. those which met consensus criteria in the e-Delphi study but were not recommended for inclusion in the COMPACT core outcome set, are given in Table 6.

Discussion

This study identified mandatory and optional core clinical outcome measures for inclusion in the future CRPS international research registry. A comprehensive literature review informed an initial list of outcomes that was reviewed and refined in a workshop with physicians, therapists and researchers from across the CRPS community. Using a 2-Round e-Delphi consensus process, a long-list of 59 outcomes was reduced to nine potential outcomes for inclusion. A final consensus workshop to consider feasibility and acceptability of each outcome resulted in recommendation of the inclusion of two core outcomes (record of current CRPS medications and PTSD) and a further two optional research outcomes (allodynia mapping and temperature difference between limbs).

Our findings indicated outcome item ratings were broadly consistent across different professional groups: physicians/surgeons, researchers, and nurses/therapists, albeit with a trend towards nurses/therapists rating the relevance of psychological and emotional outcomes more frequently. Previous studies of core outcome sets have similarly found that, whilst there may be variations detected when subgroups of stakeholders are considered separately, there is also overlap across groups [3,26].

Whilst the COMPACT consortium has already published a core set of *patient-reported* outcome measures [16], no other recommendations for a core clinical outcome set for CRPS studies have been identified to date. This study presents pragmatic, consensus-driven, recommendations to address this gap, however there were some limitations. Firstly, invitations to participate only went to members of the IRC and IASP SIG. Whilst these groups are multi-disciplinary and representative of those with a particular interest in CRPS, it is

plausible that others with expertise in CRPS, but not members of these specific communities, were excluded from the process. Secondly, the e-Delphi survey was presented in English language only and this may have limited responses from those for whom English was not a familiar language.

Whilst the e-Delphi process had identified nine potential outcome measures, only two were determined to be feasible and pragmatic for inclusion as mandatory outcomes, one of which is reliant on patient report. Two outcomes were recommended as optional, due to potential constraints of measurement across study centres. Whilst the practical factors leading to these decisions were discussed and debated thoroughly within the core study team, these conclusions were not referred back for consultation with a wider group of clinicians and academics working in the field of CRPS. To mitigate this limitation, it will be prudent in the implementation of the future CRPS international research registry to periodically invite feedback from contributors to ensure the outcomes requested for input into the data set continue to remain feasible and pragmatic to collect.

This study has identified the core clinical outcomes for inclusion in the future CRPS international research registry and has established a basis for consistency and fidelity of data collection. However, future work is needed to determine exactly how these clinical outcomes can best be measured and recorded. For example, although the PTSD-8 has been validated for use in chronic pain, further assessment will be necessary to determine its psychometric properties in people with CRPS and to develop normative data for use in this population. Similarly, the development of a new COMPACT body-mapping allodynia tool will be subject to pilot testing for feasibility, acceptability and validity prior to its full adoption.

The frequency of recording of outcome data in the future CRPS international clinical research registry will also be set within the registry protocol. Translation of data collection protocols, the PTSD questionnaire and the electronic data capture tool (ALEA) is planned to ensure global accessibility of this core set. Forward and backwards translation will be undertaken by COMPACT consortium research partners in each relevant country and will adhere to the "best practice" translation standards previously used by members of the study team [20].

This study used a robust consensus methodology to make recommendations for a minimum set of core clinical outcomes to be used as data fields in a future international research registry and data bank. These will complement the already agreed patient reported outcome measures within the registry. Development and testing of data measurement and capture processes are underway. Once established, the registry will provide a large and consistent set of CRPS outcome and demographic data that will advance our understanding of the presentation, course, and management of CRPS.

Acknowledgements

Conflict of Interest Statement

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Table 1: The 44 items presented at 2018 Boston meeting, indicating those retained and rejected as a result of consultation during the meeting and subsequent expert opinion.

ITEMS RETAINED	REDEFINED / RENAMED AS
Activity	Level of activity
Allodynia	Degree and extent of brush-evoked allodynia
Analgesic consumption	Name and dosage of current medications
Body Perception Disturbance	Description of patient's global body perception (plus additional items*)
Bone measures	Assessment of bone density (plus bone turnover added*)
Dysynchiria	Presence / absence of dysynchiria (plus synchiria added*)
Endothelial function	Quantitative assessment of changes in vascular perfusion
Genetic characteristics	Genetic profiling (plus family history items added*)
Grip strength	Grip strength performance
Heart rate variability	Assessment of cardiac performance
Heat threshold(s)	Heat detection threshold (plus additional thermal pain items*)
Hyperalgesia	Degree and extent of hyperalgesia
Inflammatory mediators	Inflammatory mediators
Limb laterality	Accuracy in limb laterality recognition task
Lower limb function	Standardised therapy assessment of lower limb function (plus additional functional items*)
Neuropsychological function	Clinical assessment of executive function
Other physiological	Record of diagnosed physical co-morbidities
Pain (clinician rated)	Temporal summation of pain (plus additional clinical pain measures*)
Psychological	Record of diagnosed psychological co-morbidities (plus additional items*)
Range of motion	Degree of active and passive joint range of movement
Skin colour	Nature and extent of skin changes
Skin temperature	Quantitative assessment of skin temperature
Sweating	Quantitative assessment of degree of sweating
Swelling	Quantitative assessment of volume of swelling
Vibration threshold	Vibration detection threshold (plus vibration pain threshold*)
Visual function	Visual performance
Walking ability	Performance in timed walking test

ITEMS REMOVED	REASON
Blood sampling	Considered out of scope due to measurement dependencies
Cutaneous vasoconstriction	Range of vasomotor items retained and considered sufficient
Femoral angle	Standard therapy assessment items added*
Finger flexion	Standard therapy assessment items added*
General function	Range of specific physical function items added*
Intestinal permeability	Considered out of scope as a potential core item
Motor function	Range of specific physical function items added*
Muscle force	Range of specific physical function items added*
Parietal lobe function	Considered out of scope due to measurement dependencies
PET/MRI/CT scanning	Considered out of scope due to measurement dependencies
QST other	Specific sensory perception items added*
Radiographic measures /ultrasonography	Specific quantitative assessment items added*
Regional inflammation	Inflammatory mediators item retained and considered sufficient
Sympathetic skin response	Specific vasomotor items retained and considered sufficient
Temporomandibular index (TMI)	Not routinely measured in CRPS
Temporoparietal cortex function	Specific body schema items added*
Trophic changes	Specific trophic change items added*

* See italicised items in Table 2 for clinical outcomes added.

Table 2: Categories incorporating 59 items as presented in e-Delphi survey *(items in italics were added in response to the Boston workshop and subsequent expert opinion)*

Category	Item												
1. Body schema / body image	Description of patient's global body perception	*Accuracy of finger identification*	*Extent of neglect of affected limb*	Accuracy in limb laterality recognition task	*Presence and location of referred/ dual sensations*	*Accuracy of perception of body mid-line*	*Presence / absence of desire for amputation of affected limb*	*Accuracy of limb position sense*	*Presence/ absence of synchiria*	Presence/ absence of dysynchiria			
2. Co-morbidities	Record of diagnosed physical co-morbidities	Record of diagnosed psychological co-morbidities											
3. Family history	*Record of chronic pain disorders in first degree relatives*	*Record of CRPS in family*											
4. Pain & other sensory perception	Degree and extent of brush-evoked allodynia	Degree and extent of hyperalgesia	Heat detection threshold	*Heat pain threshold*	*Cold detection threshold*	*Cold pain threshold*	Vibration detection threshold	*Vibration pain threshold*	*Two-point discrimination*	*Mechanical pain threshold*	*Pressure pain threshold*	Temporal summation of pain	*Hearing performance* / Visual performance
5. Physical function	Level of activity	Degree of active and passive joint range of movement	*Presence/ absence of joint hypermobility*	Performance in timed walking test	*Performance in timed sit-to-stand test*	Standardised therapy assessment of lower limb function	*Finger tap rate*	*Performance in 9-hole peg test (upper limb)*	Grip strength performance (upper limb)	*Pinch strength performance (upper limb)*	*Standardised therapy assessment of upper limb function*		
6. Physiological	Genetic profiling	Assessment of cardiac performance	Inflammatory mediators	*Nerve conduction performance*									
7. Medications	Name and dosage of current medications												
8. Psychological	*Clinical assessment of anxiety*	*Clinical assessment of depression*	*Clinical assessment of PTSD*	Clinical assessment of executive function	*Clinical assessment of childhood trauma*	*Clinical assessment of adulthood trauma*							
9. Trophic changes	Nature and extent of hair changes	Nature and extent of nail changes	Nature and extent of skin changes	Assessment of bone density	*Assessment of bone turnover*								
10. Vasomotor dysfunction	Quantitative assessment of skin temperature	Quantitative assessment of volume of swelling	Quantitative assessment of degree of sweating	Quantitative assessment of changes in vascular perfusion									

Table 3: Demographic characteristics of e-Delphi survey participants

	Round 1 n=74	Round 2 n=60
Respondents' Professions		
Nurse	2 (3%)	1 (2%)
Occupational Therapist	1 (1%)	1 (2%)
Physician	44 (60%)	31 (51%)
Physiotherapist	9 (12%)	9 (15%)
Psychologist	1 (1%)	1 (2%)
Researcher	14 (19%)	14 (23%)
Surgeon	3 (4%)	3 (5%)
Clinician or Academic?		
Academic	10 (13%)	10 (17%)
Clinician	25 (34%)	18 (30%
Clinical Academic	39 (53%)	32 (53%)
Length of time working in the field of CRPS		
Less than 1 year	1 (1%)	0 (0%)
1-5 years	13 (18%)	11 (18%)
6-10 years	15 (20%)	12 (20%)
11-15 years	9 (12%)	7 (12%)
16-20 years	10 (14%)	8 (13%)
More than 20 years	26 (35%)	22 (37%)
Average number of cases of CRPS seen per month[a]		
Fewer than 1	9 (14%)	7 (14%)
1-5	28 (44%)	22 (44%)
6-10	16 (25%)	11 (22%)
11-15	4 (6%)	4 (8%)
16-20	4 (6%)	3 (6%)
More than 20	3 (5%)	3 (6%)
No of respondents by geographical area worked in		
Europe	26	23
North America	28	21
Central and South America	7	5
Asia	1	1
Australasia	11	9
Africa	1	1
Total number of countries represented	23	21

[a]This question was only available to respondents who were clinicians or clinical academics

Table 4: Items meeting the consensus criterion* (median score of ≥7 on a 1-9 scale as rated by 75 % of respondents) in Round 1 and Round 2

	Round 1 group median score	Round 1 % of respondents rating item as ≥7	Round 2 group median score	Round 2 % of respondents rating item as ≥7
Record of diagnosed psychological co-morbidities	8	78.38*	8	86.67*
Degree and extent of brush-evoked allodynia	8.5	87.84*	8	86.67*
Degree and extent of hyperalgesia	8	87.84*	8	88.33*
Level of activity (as determined by wearable devices)	8	74.32	8	85.00*
Name and dosage of current medications	8	78.38*	8	85.00*
Clinical assessment of anxiety	8	77.03*	8	86.67*
Clinical assessment of depression	8	79.73*	8	86.67*
Clinical assessment of Post-Traumatic Stress Disorder	8	74.32	8	86.67*
Quantitative assessment of skin temperature	8	68.92	8	78.33*

	Round 1 group median score	Round 1 % of respondents rating item as ≥7	Round 2 group median score	Round 2 % of respondents rating item as ≥7

Table 5: Round 2 group median scores for all e-Delphi items, including % of respondents rating item as ≥7. Shaded items are those that met the consensus criterion (median score of ≥7 on a 1-9 scale as rated by 75 % of respondents).

	Round 2 group median score	Round 2 % of respondents rating item as ≥7
Body schema / body image		
Description of patient's global body perception	7	63.33
Accuracy of finger identification	5	11.67
Extent of neglect of affected limb	7	61.67
Accuracy in limb laterality recognition task	6	31.67
Presence and location of referred/ dual sensations	6	26.67
Accuracy of perception of body mid-line	5	20.00
Presence / absence of desire for amputation of affected limb	6	30.00
Accuracy of limb position sense	6	48.33
Presence/ absence of synchiria	4	18.33
Presence/ absence of dysynchiria	5	20.00
Co-morbidities		
Record of diagnosed physical co-morbidities	7	65.00
Record of diagnosed psychological co-morbidities	8	86.67
Family history		
Record of chronic pain disorders in first degree relatives	6	35.00
Record of CRPS in family	7	58.33
Pain and other sensory perceptions		
Degree and extent of brush-evoked allodynia	8	86.67
Degree and extent of hyperalgesia	8	88.33
Heat detection threshold	6	35.00
Heat pain threshold	6	36.67
Cold detection threshold	6	31.67
Cold pain threshold	6	38.33
Vibration detection threshold	5	25.00
Vibration pain threshold	5	25.00
Two-point discrimination	6	43.33
Mechanical pain threshold	7	63.33
Pressure pain threshold	7	63.33
Temporal summation of pain	6	36.67
Hearing performance	3	8.33
Visual performance	3	6.67
Physical function		
Level of activity	8	85.00
Degree of active and passive joint range of movement	8	73.33
Presence/ absence of joint hypermobility	5	15.00
Performance in timed walking test (lower limb)	6	33.33
Performance in timed sit-to-stand (lower limb)	5	18.33
Standardised therapy assessment of lower limb function	6	23.33
Finger tap rate (upper limb)	5	15.00
Performance in 9-hole peg test (upper limb)	5	10.00
Grip strength performance (upper limb)	6	41.67
Pinch strength performance (upper limb)	6	33.33
Standardised therapy assessment of upper limb function	6	35.00
Physiological		
Genetic profiling	5	18.33
Assessment of cardiac performance	3	1.67
Inflammatory mediators	7	53.33
Nerve conduction performance	5	21.67

Medications		
Name and dosage of current medications	8	85.00
Psychological		
Clinical assessment of anxiety	8	86.67
Clinical assessment of depression	8	86.67
Clinical assessment of Post-Traumatic Stress Disorder	8	86.67
Clinical assessment of executive function	6	33.33
Clinical assessment of childhood trauma	7	53.33
Clinical assessment of adulthood trauma	7	61.67
Trophic changes		
Nature and extent of hair changes	7	65.00
Nature and extent of nail changes	7	60.00
Nature and extent of skin changes	7	66.67
Assessment of bone density	6	28.33
Assessment of bone turnover	5	18.33
Vasomotor dysfunction		
Quantitative assessment of skin temperature	8	78.33
Quantitative assessment of volume of swelling	7	63.33
Quantitative assessment of degree of sweating	7	60.00
Quantitative assessment of changes in vascular perfusion	6	35.00

Table 6: Final consensus on the inclusion/exclusion in COMPACT of potential clinical outcomes

	Consensus decision	Rationale
Record of diagnosed psychological co-morbidities	Exclude	• Diagnosed psychological co-morbidities are impractical to collect in standard clinical practice • Patients may not be able to accurately recall prior consultations, or may not be aware of having previously received a diagnosis • There can only be low confidence of any prior diagnosis having been based on DSM criteria
Degree and extent of brush-evoked allodynia	Include map of allodynia as an optional research item	• The degree and extent of brush evoked allodynia is time-consuming to assess • The presence/absence of allodynia is already included as a clinical outcome in the CRPS Severity Score • Mapping allodynia is recommended as an optional research outcome via a simple body map tool
Degree and extent of hyperalgesia	Exclude	• The presence/absence of hyperalgesia is already included in the CRPS Severity Score and this is considered sufficient for the CRPS registry
Level of activity (as determined by wearable devices)	Exclude	• Assessment of level of activity is difficult to standardise across centres • Providing all patients with wearable devices has cost and resourcing implications • Wearing a monitoring device has, in itself, potential to lead study participants to change exercise behaviours
Name and dosage of current medications	Include as a core clinical item	• A record of the name and dosage of current medications is recommended as a core clinical outcome (current = all medications for CRPS and other conditions being taken by the patient at the time of clinical assessment) • The record can include CRPS medications taken previously, but discontinued
Clinical assessment of anxiety	Exclude	• The COMPACT patient-reported outcome set already includes standardised and validated patient-reported measures of anxiety and is considered sufficient for the purposes of the future CRPS registry
Clinical assessment of depression	Exclude	• The COMPACT patient-reported outcome set already includes standardised and validated patient-reported measures of depression and is considered sufficient data for the purposes of the future CRPS registry
Clinical assessment of Post-Traumatic Stress Disorder	Include as a core patient-reported item	• Assessment of PTSD is by completion of self-report of current symptoms • To add a brief standardised outcome measure as a core item in the patient-reported core outcome set
Quantitative assessment of skin temperature	Include as an optional research item	• Thermographic assessment is difficult to standardise across centres • Not all centres have access to thermal imaging equipment • Calibration of thermometers is not possible across centres, therefore absolute temperatures are not comparable across centres • The temperature differential between the CRPS-affected and non-affected limb, measured using an infrared thermometer, is recommended as an optional research outcome.

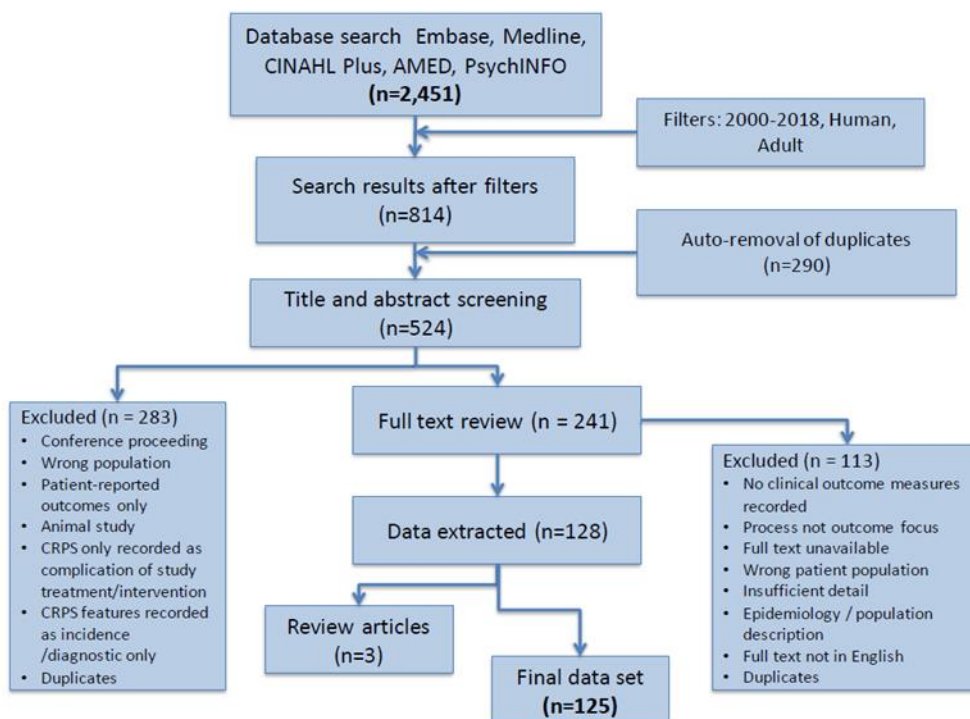Figure 1. Systematic Literature Review process

Figure 2: e-Delphi survey format

Figure 3: Round 2 item ratings by profession (rated as ≥7 by 75% of respondents within the group)
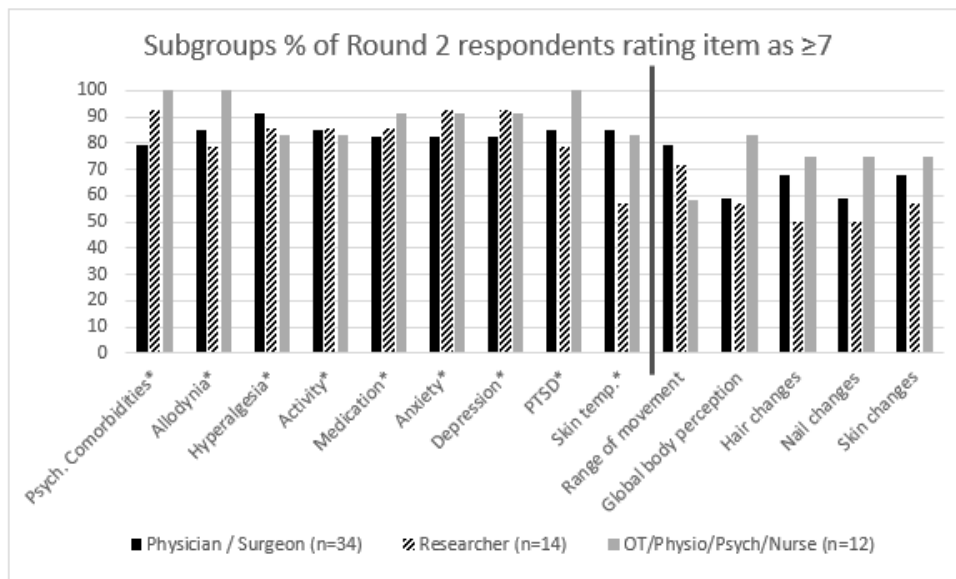
* These items met the overall consensus criteria across whole dataset. The solid vertical line represents the consensus criterion of a median score of ≥ 7 as agreed by 75% of the study group. Remaining items, whilst meeting the criterion within their professional subgroup, did not meet the consensus criteria overall.