A multi-centre study to explore the feasibility and acceptability of collecting data for Complex Regional Pain Syndrome clinical studies using a core measurement set. Study protocol*

Abstract

Objectives

This international, multi-centre study will inform the final data collection tools and processes which will comprise the first international, clinical research registry for Complex Regional Pain Syndrome (CRPS). This study will; (1) test the feasibility and acceptability of collecting outcome measurement data using a patient reported, questionnaire core measurement set (COMPACT); (2) test and refine an electronic data management system to collect and manage the data.

Methods

A maximum of 240 adults, meeting the Budapest diagnostic clinical criteria for CRPS type I or II, will be recruited across eight countries. The COMPACT questionnaire will be completed on 2 occasions; at baseline (T1) and 6 months later (T2). At T2 participants will choose to complete COMPACT using a paper or electronic version. Participants will be asked to feedback on their experience of completing COMPACT via a questionnaire. A separate questionnaire will ask clinicians to feedback their experience of data collection.

Analysis

The study is not aiming to derive statistically significant data but to ascertain the practicalities of collecting data, using the COMPACT questionnaire set, across a range of different cultures and populations. At the end of the study, a single workshop will be convened to review the findings and agree the final documents and processes for the international registry.

Key words: Complex Regional Pain Syndrome; core measurement set; registry; clinical studies; patient reported outcomes.

***Trial registration number**: ISRCTN33817530

1. Introduction

Complex Regional Pain Syndrome (CRPS) is a persistent pain condition, usually affecting a limb, and characterised by a range of sensory, motor, trophic and autonomic abnormalities (Marinus et al, 2011). There are two types of CRPS categorised by the absence (type I) or presence (type 2) of a lesion to a major nerve, with the latter presenting less commonly. Incidence rates of CRPS are low and range from 5.46 to 26.2 per 100,000 person years (de Mos, 2007; Sandroni et al, 2003). As a consequence, multi-centre collaborative research is needed to achieve sufficient sample sizes for meaningful studies. In addition, the multidimensional nature of CRPS means that clinical trials currently use a diverse range of questionnaire outcome measures (Grieve et al, 2015) and this has been a limiting factor in our understanding of the cause, course and optimum management of CRPS.

To address this, an international consortium of patients, clinicians, researchers and industry representatives was established in 2013 with the long-term aim to establish an international, clinical research registry for CRPS. The acronym COMPACT was adopted by the consortium to represent the initiative; 'Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies'. The consortium currently comprises membership from 20 countries* and participation in the project work is via international workshops, teleconferences and digital communications. XXXXXXXXXXXXXXXXXXXXXXXX, UK is the lead centre for this work.

*COMPACT membership: Australia, Argentina, Brazil, Canada, Denmark, France, Germany, India, Israel, Japan, New Zealand, Netherlands, Norway, Pakistan, Russia, South Korea, South Africa, Switzerland, United Kingdom, United States.

Clinical research registries are widely used in many rare conditions (Dasenbrook and Sawicki, 2018; Psoter and Rosenfeld, 2013; Villa-Blanco and Calvo-Alén, 2012) and provide a means of collating a large, uniform set of observational, retrospective data across a wide geographical area (Psoter and Rosenfeld, 2013). Establishing an international, clinical research registry for CRPS has long term importance in relation to the prevention of CRPS

and the provision of targeted treatments. As the largest database of CRPS outcome and demographic data, the registry will enable researchers to access a consistent, international dataset which will be used to gain a better understanding of the potential phenotypes of CRPS, risk factors and targeted treatment approaches. Only by establishing a data set of this size and diversity can researchers identify those factors which may precipitate CRPS, and thereby develop preventative strategies. In addition, with a better understanding of the mechanisms of CRPS, rehabilitation therapies can adopt a targeted approach.

The first stage in establishing the registry was to define a minimum core set of standardised, patient-reported, questionnaire outcome measures which would be at the heart of the dataset. This was described as the COMPACT questionnaire set. A core outcome measurement set can be defined as an agreed, standardised set of outcomes which should be measured and reported in all clinical trials in a particular condition (Williamson et al, 2012). Through a series of workshops and supplementary work, the consortium agreed, and published, the core set of questionnaire outcome measures, which was recommended for use in future CRPS clinical studies in an adult population (Grieve et al, 2017). The defined measures captured the domains within the over-aching research question ‘What is the clinical presentation and course of CRPS and what factors influence it?’ and comprised; pain, disease severity, participation and function, emotional and psychological function, self efficacy, catastrophizing and patient's global impression of change (Grieve et al, 2017). One clinician-reported measure captured the severity of CRPS (Harden et al, 2017). A Delphi study, led by consortium members, is currently being conducted to define the core clinical outcome measures which will be included in the registry but this is not described in this protocol.

The final COMPACT registry will comprise;

- Demographic data
- Patient-reported questionnaire outcome measures (COMPACT) and one clinician-reported questionnaire outcome measure (Grieve et al (2017)

- Core clinical outcome measures (to be defined)

The ALEA electronic data capture system, provided by FormsVision BV and administered by a team from the Clinical Informatics Research Unit (CIRU) at the University of Southampton, UK, will be used to collect and manage the registry data. ALEA is widely used in clinical trials internationally. A bespoke COMPACT registry has been developed by the CIRU team, using this platform.

COMPACT is a project adopted by the CRPS IRC (International Research Consortium); an organisation that facilitates the pooling of resources for timely and conclusive studies (http://www.crpsconsortium.org). We anticipate that in the long term, the utilisation of a COMPACT registry will aid us in the potential prevention of CRPS; the reduction of healthcare costs via more timely and effective care; and the design of new therapeutic interventions and rehabilitation techniques, which will reduce pain and disability and help people lead more active lives.

Prior to the COMPACT registry being widely utilised to capture the core patient reported questionnaire outcome measures, it is necessary to test the feasibility of collecting these data across representative groups within an international CRPS population. We also wish to establish that it is feasible for data from international centres to be collected and managed using the online ALEA data management system. This will ensure that the registry is a robust means of data capture before the core clinical outcomes measures are included.

2. Aims of the current study

The aims of this study are to test the feasibility and acceptability of collecting outcome measurement data using the agreed COMPACT questionnaire set in the international CRPS population, in order to inform an optimum protocol for the final registry. We also wish to test and refine the ALEA electronic data management system to collect and securely manage these data. We will devise the final registry data collection tools and processes based on information gained.

The objectives of the feasibility study are:

1. To establish and test relevant research governance, institutional and ethical procedures required for the routine use of COMPACT.
2. To test the feasibility of the recruitment process and study procedures across a representative group of future participating centres.
3. To establish if data collection using COMPACT is acceptable to clinicians and patients and to resolve any issues during the development phase.
4. To establish what proportion of data is missing from each completed questionnaire and to identify strategies to optimise data completion (target = < 10% missing data).
5. To determine the optimum data collection time points to inform a future protocol.
6. To determine the quantity of time required by researcher and clinician for recruitment and data collection.
7. To identify a fully functioning and secure electronic data management system and to test data entry and storage processes with demonstration and feasibility study data.

3. Methods

3.1 Study design

This is a multi-centre feasibility study conducted in CRPS populations in multiple countries, to test the feasibility and acceptability of collecting outcome measurement data using a paper and electronic version of the COMPACT questionnaire set (Figure 1).

Insert Figure 1.Trajectory of study protocol

3.2 Study population

Data will be collected from patients at research centres in eight countries; UK, Switzerland, Canada, Israel, Japan, United States of America, Australia and Brazil, to represent the diversity of countries who may wish to use COMPACT in the future. Each centre will collect ≥ 10 (maximum 30) complete Time 1(T1) and Time 2 (T2) COMPACT data sets which we anticipate will take between 12 and 15 months. T1 is at baseline and T2 at 6 months (+/- 2 weeks).

COMPACT will be advocated for use in adult clinical study populations and therefore we will recruit patients ≥ 18 years with CRPS I or II, meeting the Budapest diagnostic clinical criteria (Harden et al, 2010), who are attending for a face to face clinical visit. The broad inclusion criterion (see below) ensures a wide range of subjects will be recruited to represent different ages, disease durations, gender, ethnicity and COMPACT access requirements. People who are unable to understand the written word or unable to write, and/or unable to give informed consent will be excluded.

3.3 Identification of potential participants and recruitment

Patients attending the participating study centres will be identified by the local multi-disciplinary team as potential recruits to this study. This can be at any point in their treatment pathway. A member of the multidisciplinary team undertaking the routine clinical visit will provide potential participants with a recruitment pack which will include; an invitation letter, a participant information sheet, two copies of the consent form (one is for the patient's own records), the baseline COMPACT questionnaire and a contact details form to enable the participant to be contacted at the second time point. Each centre will include a pre-paid envelope if applicable. The individual is invited to consider the information in the recruitment pack and decide whether they wish to participate in the study. At this point an opportunity for questions or discussion will be available with a member of the research team; face to face or via an identified telephone or email contact. Informed consent will be obtained by the return of a signed and dated consent form to the local team. This will include consent to provide their contact details (address and/or email) to enable them to be contacted regarding data collection at T2. Those who wish to participate are asked to select in which format, paper or electronically, they wish to receive the questionnaire at T2. To inform a future protocol those who choose not to participate, and are willing to give a reason, are invited to complete the free text section on the contact details form. This can be returned anonymously in the pre-paid envelope. Patients will be accepted on to the study whenever the COMPACT documents are returned. Each centre will be asked to record the number of recruitment packs distributed. This will be compared with the actual number of patients recruited to provide information regarding recruitment methods and rates.

3.4 Data collection tools

The data collection tools comprise two documents;

1. The patient reported COMPACT questionnaire set, completed at baseline and at 6 months, comprising standardised, outcome measures (Table 1). Where applicable, we have obtained permission from the distributors or licence holders to use the standardised questionnaires for the purposes of this study.

Insert Table 1: Patient reported outcome measures included in COMPACT

2. The CRPS Severity Score (CSS) (Harden et al, 2017)

This will be completed by the clinician and is directly derived from the Budapest CRPS diagnostic criteria (Harden et al, 2017). This is a routine data collection tool that is used by a clinically qualified healthcare professional to confirm the diagnosis of CRPS. The CSS will be completed at baseline and the data will only be included in the study if the patient completes the COMPACT documentation and gives informed consent. It will also be completed at T2 if a study patient attends a clinical appointment at this time. Symptoms reported by the individual and CRPS signs present on examination by the clinician, are recorded by the clinician and added to give a total. Higher scores indicate greater CRPS severity (range 0-16) (Harden et al, 2017).

3.5 Data collection

Data will be collected at two time points. The instructions in the participant information sheet will ask potential patients to complete the questionnaire on a single day, if possible, so that the information is representative of their health at a specific time point.

3.5.1 Data collection at T1

At T1 this will comprise the paper version of the baseline COMPACT questionnaire set, and the CSS which is completed by the clinician. Baseline is defined as the time at which the patient is recruited to the study by signing the informed consent document. This can be at any time in their CRPS

pathway. At T1, the patient will select one of the two options of data collection at Time 2; 1) paper or 2) via the ePRO platform of the ALEA electronic data management system.

3.5.2 Data collection at T2

At T2 (+/- 2 weeks) participants will be sent a second COMPACT questionnaire set in the format they selected at T1. This differs to baseline, only by collecting less demographic data and includes a patient global impression of change.

For those selecting receipt of a paper version, the T2 patient reported questionnaire and an accompanying letter will be sent to patients by post shortly before the 6 month time point. A pre-paid envelope will be supplied, for return to the local study team. Alternatively, if the patient has a clinical visit scheduled at the 6 month time point, the above documents may be given to the patient at this visit and the CSS will be completed by the clinician. The CSS will be accepted at T2 if it is completed +/- 2 weeks of the patient COMPACT questionnaire set T2 completion date. If the CSS is not completed at Time 2, the researcher will record the reason, for example; no clinical visit scheduled; outside +/- 2 week window.

Approximately two weeks before the 6 month time point, those patients who wish to complete the T2 questionnaire electronically, will receive an email containing a link which will allow access to ALEA's electronic Patient Reported Outcome (e-PRO) environment (https://prod.tenalea.net/ciru/ePRO/). Instructions will be supplied for the patient on how to complete the questionnaire via a computer, tablet or smartphone. Text preceding the questionnaire will re-familiarise the patient with the study.

At Time 2, if COMPACT is not completed online or returned by post within 14 days, one reminder letter will be sent by post or email.

3.5.3 Feedback on the data collection experience by research patients

At Time 2, at each centre, patients will be invited to complete a short feedback

questionnaire to ask them about their experience of completing the questionnaires, for example; the time taken to complete, the layout, ease of accessing the questionnaire electronically. The final content of the feedback questionnaire will be informed by the data collection process, and by matters that have arisen in the Project Management Group's regular meetings. Patient feedback will be collected on paper or electronically according to the patient's preference. Responses will be anonymised and, where applicable, they will be translated into English prior to analysis of the data by the XXXXX administrative centre. Consent to this data collection will be implied by the submission of a completed questionnaire.

3.5.4 Feedback on data collection experience by clinicians

A short questionnaire will be sent by email from the lead centre (XXXXX, UK) to the principal investigator at each centre asking clinicians about their experience of data collection. The questions asked will be informed by matters that have arisen in the Project Management group's regular meetings. It will invite feedback to include; the time required by the clinician for data collection at each time point; the ease of the process.

3.6 Data management

At Time 1, data comprising CSS, patient contact details and the patient-reported COMPACT baseline questionnaire will be entered directly on to ALEA by the local researcher. At Time 2, the local researcher will enter the CSS data (if applicable) and, if the patient has chosen to complete the paper version, the COMPACT follow up questionnaire, directly on to ALEA. Patients selecting receipt of the electronic version of COMPACT will complete the questionnaire directly on to the ALEA online platform.

4. Analysis

The study is not aiming to derive statistically significant data but to ascertain the feasibility and acceptability of collecting data, using the COMPACT questionnaire set, across a range of different cultures and populations. Data will be collated on patient recruitment, including total number of patients recruited per centre; consent rate; participation rate; loss to follow-up; percentage response to COMPACT questions. Key findings from the patient

feedback questionnaires will be identified and synthesised to inform the final documents and processes. This will include consideration of key difficulties and commonalities across study centres. Topic areas within the patient feedback questionnaire data, and responses from the clinician questionnaires, will determine the acceptability of data collection processes and data collection timings.

A single workshop will be convened to review the findings of this feasibility study when all participants, at each research centre, have completed Time 2. For the convenience of those attending, this ideally will run alongside an international meeting. The attendees will comprise COMPACT group members; patients, clinicians, researchers and representatives from industry. The final documents will be agreed through consensus. The process for registering with COMPACT, seeking ethical approvals, translation processes, data collection and data management will be finalised. Any other pertinent issues identified from the findings will also be agreed.

5. Study monitoring

A project management group has been established and comprises: a patient representative from each centre where possible, the Principal Investigator from each centre and the UK administrative team. The group will convene approximately every 6 months via teleconference to review study progress. A newsletter will be produced approximately every 3 months and distributed via email to each study centre. This will report on recruitment and pertinent study issues.

6. Patient and public involvement

Patient representatives, from the UK, Netherlands and Switzerland, are members of the COMPACT consortium and contributed to the development of the COMPACT core measurement set. A patient representative from the UK is a member of the project management group for this feasibility study and additional patient representatives will be recruited from each international site where possible. Patient representatives will be invited to the workshop where the final documents and processes will be agreed. Patient representatives may be asked to be co-authors of resultant publications if appropriate,

dependent on their level of involvement in the study. The study team are committed to involving patients and the public in research and are guided by INVOLVE's recommendations (https://www.invo.org.uk/resource-centre/resource-for-researchers/).

7. Data confidentiality and archiving

Data will be collected and retained in accordance with local laws and regulations, for example the General Data Protection Regulation (GDPR) (ICO, 2018), in the UK. Study documents will be retained in a secure location at each research centre during and after the study has finished.
The research data will be anonymised at the point of data collection and any patient identifiable details held electronically (contact details and links to subject number) will be password protected to ensure these are only available to the patient's local study centre and XXXXX, as the administrative centre.

During the study, all data will be reported in pseudonymised form and will be identified by the assigned subject number. Individual centres will only have access on ALEA to data collected via their specific centre, including that which links a patient to their assigned subject number. XXXXX, as the administrative centre, will have access via ALEA to all data including the patient identifiable details, from all international centres.

Each patient will have an electronic record known as an electronic Case Report Form (eCRF). Study eCRFs will be accessed remotely via a web browser. Only users authorised by XXXXXXXXXXXXXXXXX, UK, will have access to the eCRFs. Individual centres will only have access to the data for their centre. Access to the servers will be limited to ALEA personnel.
After the data set has been closed, and the primary analysis completed, each participating country will have access to their data only. The administrative centre, XXXXXXXXXXXXXXXXXXXXXXXXXX, will have access to the entire dataset.

Each study centre will be responsible for the dissemination and collection of paper study documentation relating to the patients at their centre. This will be directly from the study patients using stamped addressed envelopes or by

hand. All paper documentation (identifiable and non-identifiable) will be stored securely at the relevant study centre. These documents will be stored in locked cabinets within the study centre for each country, and will remain in that country.

ALEA consists of a study design (SD) component and a data management (DM) component. During setup and maintenance of the study, the SD component is used to create or modify the design of the study. The DM component exists on a test/development, acceptance and production instance. The test/development instance provides an environment to test the setup and modifications for the CIRU programmers. The acceptance instance is used by XXXXX, the administrative centre, for user acceptance testing. The production instance is used once the study is live. These environments are physically isolated, and do not share data and accounts.

Study design and the test/development environment of data management are hosted in Amsterdam, the Netherlands. The acceptance and production environments of DM are hosted in Den Bosch. This location is a secured, ISO 27001 certified data centre operated by InterConnect BV in Den Bosch, the Netherlands. FormsVisions' Quality Assurance includes formal disaster management procedures for management of issues related to the operational environment. The data held in secure servers in the Netherlands is backed up daily.

8. Ethical and legal considerations

All patients will continue to receive routine care and any voluntary involvement in the study will be in addition to that care. There are no particular risks to patients in this study but there may be some emotional stress evoked in completion of the questionnaires. These will require patients to consider their current health status which may evoke negative feelings. We do not anticipate that these emotions will be any different than those evoked when completing health outcome measures in the routine clinical setting. The Patient Information Sheet contains a statement that advises patients to speak to their family doctor or a member of the local research team, if the questionnaire has raised any concerns or issues. If a

member of the local research team is contacted, they will refer on to the team clinical psychologist if required. A disclaimer within the consent form informs patients that their responses to the questionnaire will not be scrutinised by a medical professional.

It will be made clear, both verbally and in the written study information, that if research patients feel unable to continue with the study they may withdraw at any time without this affecting their routine care. It will be made clear in the consent document that any data already collected will be included in the study; however there will be no requests for any further data.

Prior to commencement of the study, the study protocol and all other relevant documentation will be submitted for UK Research Ethics Approval and NHS Permission at the XXXXXXXXXXXXXXXXXXXXXXXX. For centres outside the UK, it will be the responsibility of the principal investigator at that centre to seek the relevant approvals including local ethical approval as per local requirements. Study documentation will not be distributed to a centre before all approvals are in place. A record of all approvals will be stored within the Master File at the UK main co-ordinating centre (XXXXX). Each principal investigator will be responsible for adhering to research governance and good clinical practice as required locally, including data protection and storage of data.

9. Translation of study documents and data

Centres with the necessary resources to collect and manage COMPACT data have been recruited, but the centres vary in terms of culture, language and healthcare organisational structures so as to offer insight into the challenges we are most likely to encounter in a future multi-national study. This approach ensures a wide range of ethical and governance requirements are also reflected.

Many of the outcome measures incorporated in the core measurement set are already available in the languages used by the participating centres. Where documents require translation these will be undertaken by the research partners in each country under strict adherence to the ‘best

practice' translation standards (Brunner et al, 2010). This uses a forwards and backwards translation approach to ensure the meaning of text is the same across each of the countries. The research team has proven expertise and track record of undertaking these translation procedures. Where there is no capacity for this work to be undertaken by the research partners, it will be out-sourced to a UK professional translation service. Where applicable, permission and translation agreements have been obtained from the licence holders or distributor of the questionnaire outcome measure.

10. Ethical approval and dissemination: The study received ethical approval from South Central- Hampshire A Research Ethics Committee: Reference number 18/SC0322. Dissemination will be via journal publications and conference presentations. To ensure that the findings are easily accessible, a lay summary will be available on the CRPS UK Clinical and Research Network website, which is an open platform for health professionals and the public (www.crpsnetworkuk.org). The study participants will be provided with a written summary of the findings, on request.

11. Funding: This study is supported by the Swiss National Accident Insurance Fund (SUVA) and the XXXXXXXXXXXXXXXXXXXXX UK.

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Table 1: Patient reported outcome measures included in COMPACT

Patient Reported Outcome Measure	Construct
Demographic data	Date of birth, gender, CRPS affected limb, limb dominance prior to CRPS, CRPS duration and participation in employment/education/ voluntary work.
PROMIS-29† and suicide ideation single item	PROMIS-29 Profile (Cella et al 2007) which assesses 7 domains, each with 4 questions; depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities. Suicidal ideation will be assessed using a single PROMIS item (Pilkonis et al 2011)
Pain intensity numeric rating scale	To measure the least and worst pain in the previous 24 hours, to capture the daily variability in its intensity.
Short-form McGill Pain Questionnaire-2 (SF-MPQ-2)	The six neuropathic items capturing the quality of pain (Dworkin et al 2009)
Pain Catastrophising Scale	To measure how catastrophising impacts on the pain experience (Sullivan et al 1995):
EQ-5D-5L	To measure health state comprising mobility, self care, usual activities, pain/discomfort, anxiety/depression (Herdman et al 2011)
Pain Self-efficacy Questionnaire	The respondent considers how confident they are performing each activity, while taking their pain into account (Nicholas 2007)
CRPS symptom questions	Eight questions asking about CRPS symptoms and based on the Budapest diagnostic criteria (Harden et al 2010)
Patient Global Impression of Change:	This will be completed at the 6 month follow up only.

†PROMIS (Patient-Reported Outcomes Measurement Information System) is a National Institute of Health (USA) funded system, which provides psychometrically sound and validated patient reported outcome measures that can be used in a wide range of chronic conditions.