COGNITIVE MULTISENSORY REHABILITATION, A NOVEL SENSORIMOTOR INTERVENTION FOR SYMPTOM REDUCTION IN COMPLEX REGIONAL PAIN SYNDROME: A FEASIBILITY STUDY

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Introduction

This protocol describes a study aimed to investigate the feasibility and appropriateness of a novel sensorimotor treatment approach called Cognitive Multisensory Rehabilitation (CMR[1-3]) for symptom reduction in people living with Complex Regional Pain Syndrome (CRPS). This study has been informed by the findings of a CRPS-patient focus group as well as clinical observations at the Royal United Hospital in Bath. The findings from this feasibility study will inform the design of larger studies to investigate the effectiveness of CMR in CRPS, offering a novel, non-drug related treatment to CRPS treatment.

Background

CRPS is a chronic pain condition of unknown aetiology that commonly occurs following trauma to a limb, although it may occur spontaneously. It is defined as type 1 or type 2, depending on whether known major nerve damage is absent or present, respectively[4]. Patients with Complex Regional Pain Syndrome commonly describe a diverse range of sensory and motor abnormalities. Sensory problems include pain to touch or the threat of touch, evoked pain, pain hypersensitivity (allodynia or/and hyperalgesia; pain due to a stimulus that does not normally provoke pain and an increased sensitivity to feeling pain and an extreme response to pain, respectively), but at the same time non-noxious sensory loss (hypoesthesia)[5]**.** Motor problems include troubles in initiating movement, weakness and reduced function amongst others[6].

Clinical features often present in people living with CRPS commonly resulting in patients having difficulty to engage with their affected limb and therefore having a detrimental effect on rehabilitation outcomes are:

- *Body perception disturbances*: the reported individual's perceived alteration of their CRPS affected body part while regarding the remainder of their body as normal[7].
- *Loss of self-ownership and amputation desire*: patients' perception that the painful limb(s) do not belong to them and the desire to amputate these body parts.
- *Allodynia*: painful response to a stimulus that does not normally produce pain.
- *Motor impairments*: including tremor, decreased range of movement, muscle weakness, and/or having the affected limb set in a sustained, fixed posture (i.e. dystonia)[6].

Sensorimotor interventions (i.e. interventions aiming to improve sensory and motor feedback of the affected limb) have shown promising outcomes on increasing perception associated with the affected limb (i.e. tactile acuity; precision with which we can sense touch[8]) and decreasing pain intensity[9,10,11]. Although its mechanisms are largely unknown, it is thought that the 'normalized' sensory and motor feedback may compete with pain stimulus resulting in pain reduction in people with CRPS[9,12]. The evidence for the effectiveness of these treatment modalities in CRPS is weak, and often focus only on pain reduction. Thus further research is required on novel sensorimotor interventions that target also other abnormalities present in CRPS (i.e. body perception disturbances, loss of self-ownership and amputation desire and motor impairments)[13].

Cognitive Multisensory Rehabilitation[14-19] is a term agreed by the International Cognitive Multisensory Rehabilitation Centre to describe a sensorimotor intervention originally developed for stroke motor rehabilitation by Professor Perfetti (1940-2020). CMR targets somatosensory and multisensory and cognitive functions through sensory discrimination exercises[1-3]. It focuses on the perception and integration of different sensory modalities (e.g. somatosensory, visual, etc.) and body parts (e.g. shoulder and hand) in order to produce purposeful, effective and accurate movements allowing an appropriate relationship with the surrounding environment.

Clinical observations from the CRPS service at the Royal United Hospital (RUH) have suggested that CMR may have an impact on symptom reduction (e.g. decreased body perception disturbances or pain reduction) as a part of a multidisciplinary rehabilitation programme.

In contrast to other sensorimotor interventions, CMR offers a comprehensive range of sensorimotor tasks targeting a wider range of sensorimotor, cognitive and body representation impaired functions in CRPS (i.e. body perception disturbances, loss of self-ownership and amputation desire, allodynia and motor impairments). In CMR, patients are guided to increase their affected limb's perception by discriminating different sensory information through the activation of cognitive processes (such as perception, attention or body representation) and mindful movements (*See figure 1*).

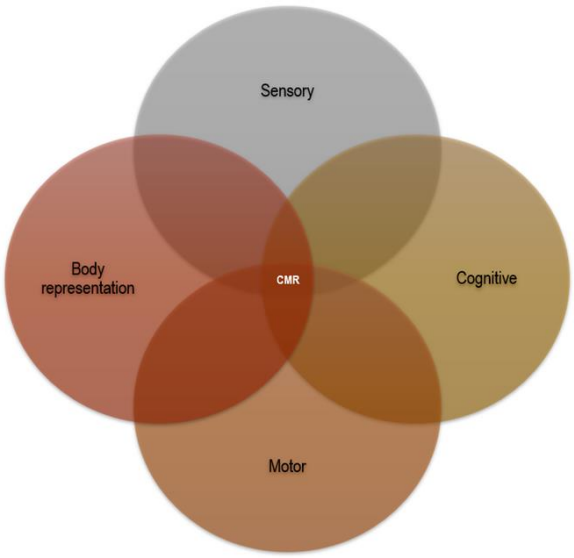

Figure 1: Cognitive Multisensory Rehabilitation components

Furthermore, unlike sensorimotor interventions, CMR tasks are considered to be discrimination-based: e.g. the patient has to recognise different types of stimuli on the painful limb, such as which fabric they feel (i.e. tactile discrimination). Because of

this, CMR interventions require a trained facilitator whose role is to help the patients to recognise the different sensory information with eyes closed by physically guiding the patient as well as posing the cognitive question. Preliminary data[10] has shown that improvements in pain levels observed following sensorimotor interventions were enhanced and lasted longer if people with CRPS discriminated between different stimuli as opposed to just receiving sensory stimulation on the painful body part. This suggested that a broader activation of cognitive processes such as problem solving, attention and perception may increase the effectiveness of sensorimotor interventions.

Recently, Covid-19 restrictions have prompted the increase of home-based treatment complementing therapy treatment. Home-based discrimination sensory retraining has shown promising results in pain reduction for people with CRPS[11].

Overarching hypothesis

Is CMR a treatment that can be adapted to treat CRPS patients in a home-based environment by a trained treatment partner?

Research questions to be answered

1. Is CMR a suitable, feasible, efficient and safe treatment intervention to treat people with CRPS in a home-based environment by a trained treatment partner?

Aims of the study

1. To identify relevant information regarding the delivery of CMR in CRPS patients in a home-based environment by a trained treatment partner, in terms of:
    a. Suitability: to determine if the intervention is appropriate for CRPS patients.
    b. Feasibility: to determine the degree to which the intervention can be easily and safely delivered by a trained treatment partner and received by a CRPS patient.

Design

A feasibility study design will be used to address the aims of this research.

Study population

CRPS patients who access the CRPS Service at the Royal United Hospital in Bath and their treatment partner (i.e. participants' relative or friend).

Study sample

A total sample of ten participants will be recruited for the study: five people with CRPS who access the CRPS Service at the Royal United Hospital and their treatment-partner (i.e. participants' husband, wife, friend, etc.). This sample is considered sufficient for this type of study to obtain enough data to meet the identified aims of this study.

Description of study population

Recruitment selection criteria

1) CRPS patients from the CRPS Service at the Royal United Hospital.

Inclusion criteria:

- Participants meet the Budapest criteria for Type I CRPS[4] (i.e. the diagnostic criteria for CRPS) in one limb (unilateral).
- Pain duration for a minimum of 3 months.
- 18 years in age or older.
- Able to understand verbal and written English.
- Willing to participate and provide written informed consent.
- Have someone available to act as treatment facilitator and consent to participate in the study.

Exclusion criteria:

- Presence of any co-morbidity that may influence CRPS symptoms including stroke, diabetic peripheral neuropathy, progressive neurological disease such as multiple sclerosis, and Parkinson's disease.
- Presence of Post-Traumatic Stress Disorder or other psychological conditions hindering patients' ability to engage with the intervention.
- Serious ill health.

2) Treatment partner

Inclusion criteria:

- 18 years in age or older.
- Able to understand verbal and written English.
- Willing to participate and provide written informed consent.
- Able to commit to delivering the treatment with the patient regularly within the home environment.

Exclusion criteria:

- Serious ill health.
- Inability to deliver the treatment due to time, physical, mental or other constraints.

3. Research procedures

3.1 Recruitment including informed consent

a) CRPS potential participants will be recruited via the following ways:

i. In the initial assessment at the CRPS Service in the RUH by the clinical multi-disciplinary team. Potential recruits will be approached by a member of the CRPS multidisciplinary team (independent from the research lead) during the initial assessment. If they are interested in participating, a recruitment pack will be handed to them.

ii. In a planned admission of patients to the CRPS residential programme. Prior to the admission in the CRPS residential programme, the CRPS administration team will send out the recruitment pack to all CRPS patients.

The recruitment pack will contain an invitation letter, participant information sheet, reply slip and freepost envelope. Alternatively, these documents can be provided electronically (i.e. by email). The recruitment pack will contain the contact details for the lead investigator.

In order to ensure those CRPS patients that have already been approached and not responded at the initial assessment are not then approached for the second time if booked on the programme, CRPS administration will keep a log of packs handed

(see appendix 4). Some patient planned admission are CRPS patients returning to the CRPS inpatient program and therefore do not go through the initial assessment route.

b) Treatment partner will be identified by the CRPS patients among friends and relatives. Once CRPS potential participants will have shown interest in participating in the study, they will be asked to provide us with the contact details of a potentially interested friend or relative. A separate recruitment pack containing will be sent to them with an invitation letter, participant information sheet, reply slip and freepost envelope and/or will provide these documents electronically (i.e. by email).

Expressions of interest in study

Having read the participant information sheet, if the CRPS potential participant is interested in the study and identifies a potential treatment partner, they will contact MPB via face-to-face/phone/reply slip or email. MPB then will contact the potential CRPS patient and treatment partner. Both CRPS patients and treatment-partner will have the opportunity to discuss any remaining queries/concerns as well as explore practical and technical issues regarding their participation in the study (e.g. total amount of practice during the intervention period, the frequency of the session and the time for the intervention to be delivered). MPB will confirm that they meet the eligibility criteria for the study.

Eligibility, screening and consent

CRPS participants and treatment partner that meet the eligibility criteria will be given a consent form (either in a physical document or in electronic format, (see form in appendix 3).

Once CRPS patients and treatment partner have given informed consent to take part in the study, they will agree with MPB on the date and time for all the sessions (Session 1, Intervention phase and Session 2) and make an appointment date for Session 1. Four copies of the signed consent form for CRPS patients and treatment partner will be made, one for the CRPS patient another for the treatment partner (to keep), one filed in the medical notes (if they are a patient at the CRPS Service) and digitally scanned and the other kept in the research site file on a password protected digital folder.

3.3 Methods

The outline of study sessions is presented in figure 2:

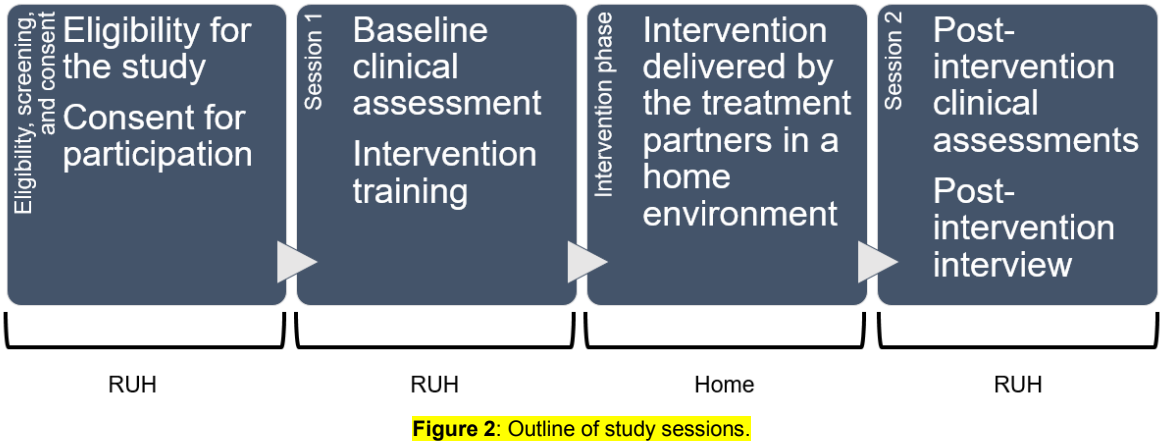

Figure 2: Outline of study sessions.

Session 1: Pre-intervention clinical assessment and Intervention Training

Session 1 will take place in a confidential clinic room at the RUH and will comprise two parts: pre-intervention clinical assessments and intervention training for treatment partner.

- **Baseline clinical assessment (Outcome measures)**

CRPS participants will be asked to fill in patient-reported outcome measures (PROMS) as follows:

Pain (Neuropathic Pain Symptom Inventory[20] and Numerical Rating Scale[21]); Pain interference (Neuropathic Pain Symptom Inventory[20]);

Neuropathic Pain Symptom Inventory[20]: The Neuropathic Pain Symptom Inventory (NPSI) is one of the most widely used tools for characterizing neuropathic pain symptom severity. The NPSI is comprised of five subscales, each representing different dimensions of neuropathic pain: burning spontaneous pain (burning), pressing spontaneous pain (pressing), paroxysmal pain (paroxysmal), evoked pain (evoked), and paraesthesia/dysesthesia. Moreover, the NPSI has good construct validity, high test–retest reliability, and good sensitivity to change in people with peripherally mediated neuropathic pain.

Numerical Rating Scale[21]: The Numerical Rating Scale (NPRS-11) is an 11-point scale for self-report of pain. It is the most commonly used unidimensional pain scale. The respondent selects a whole number (integers 0–10) that best reflects the

intensity (or other quality if requested of his/her pain. The anchors are 0 = no pain and 10 = extreme pain/worst possible pain (there are various different wordings of the upper anchor). It is often categorised into: no pain = 0, mild pain= 1-3, moderate pain = 4-6, severe pain = 7-10. Moreover NPRS has shown to be highly correlated with the Visual Analogue Scale (VAS), ranging from 0.86 to 0.95 and has a high test-retest reliability (r = 0.95)[22]

Chronic Pain Acceptance Questionnaire (CPAQ-revised)[23]. The 20-item CPAQ-revised has been designed to measure acceptance of pain. The acceptance of chronic pain is thought to reduce unsuccessful attempts to avoid or control pain and thus focus on engaging in valued activities and pursuing meaningful goals. There have been 2 factors identified in the CPAQ-Revised: (1) Activity engagement (pursuit of life activities (2) Pain willingness (recognition that avoidance and control are often unworkable methods of adapting to chronic pain). The items on the CPAQ are rated on a 7-point scale from 0 (never true) to 6 (always true). To score the CPAQ, items for Activity engagement and Pain willingness to obtain a score for each factor. To obtain the total score, add the scores for each factor together. Higher scores indicate higher levels of acceptance. CPAQ-revised has shown very good to excellent internal consistency with alphas of .82 (Activity engagement) and .78 (Pain willingness) and moderate to high correlations with measures of avoidance, distress, and daily functioning.

Kinesiophobia

Tampa Scale of Kinesiophobia[24]: The Tampa Scale for Kinesiophobia (TSK) is a 17 item questionnaire used to assess the subjective rating of kinesiophobia or fear of movement. The TSK is a self-completed questionnaire and the range of scores are from 17 to 68 where the higher scores indicate an increasing degree of kinesiophobia. The questionnaire using 4 points to assess that are based on; the model of fear-avoidance, fear of work-related activities, fear of movement, and fear of re-injury[25]. Several studies have found the scale to be a valid and reliable psychometric measure[26].

Body perception disturbance of painful limb:

The Bath CRPS body perception disturbance scale is used to measure changes in body perception of the affected limb[7]. Values of 0.66 for Cronbach's alpha and 0.87

for Cohen's kappa suggest adequate internal consistency[27,28] and adequate interrater reliability[29] of the scale.

In order to obtain the nature and extent of these perceptual disturbances the questionnaire comprises seven items covering different aspects related to the affected limb. These are: (1) a sense of ownership; (2) limb position awareness; (3) attention paid to the limb; (4) emotional feelings towards the limb; (5) perceptual disparities in size, temperature, pressure and weight (compared to the unaffected limb); (6) a desire to amputate the limb; and (7) a mental representation of the affected limb.

Five of these seven items are rated on a 0 to 10 scale to establish the extent of abnormality within that item. The sixth item determines the subjective perception of changes in size, weight pressure and temperature. The final item illustrates the mental representation of both the affected and unaffected limbs.

The final item involves an illustration of the mental representation of both the affected and unaffected limb. With eyes closed the participant generates a mental picture of both upper limbs commencing with their unaffected side. As the participant verbalises their mental image the assessor draws a picture of both limbs based on these descriptions. The resultant drawing is assessed by the participant for accuracy and truthfulness and adjusted as necessary by the experimenter following the participant's instructions. The drawing is independently graded by the experimented on a three-point scale: no distortion=0, distortion=1, severe distortion=2. If either a distortion in size or shape is depicted within the drawing, or the accompanying textual descriptions, i.e. that it is not anatomically consistent with the actual size or shape of the limb, the rating 'distortion' is given by the experimenter. A rating of 'severe distortion' is given if one or more segments of the limb are missing. The total score is calculated by summing the individual scores of the seven items[7]. The higher the score the greater is the degree of disturbance. Estimated completion time is 5 minutes. Patients' body perception disturbances will be assessed using this tool twice in total – once at the beginning of session 2 and once at the end of session 3.

Physical function PROMIS-29 v2.0 profile[30]

Evaluation of Daily Activity Questionnaire[31]: The Evaluation of Daily Activity Questionnaire (EDAQ) is a self-report assessment. It evaluates, in detail, a person's daily activity abilities with and without using ergonomic solutions (i.e. using alternate

movements and positions, activity simplification, pacing, planning, assistive devices, gadgets and equipment) or help. It includes numeric rating scales evaluating impact of conditions on e.g. pain, fatigue, mood and also 138 activities within 14 domains (sub-scales). This include: Eating /Drinking, In the Bathroom/ Personal Care, Getting Dressed/ Undressed, Bathing/ Showering, Cooking, Moving Around Indoors, Cleaning the House, Laundry / Clothes Care, Moving and Transfers, Communication, Moving Around Outside/ Shopping, Gardening/ Household Maintenance, Caring and Hobbies, Leisure and Social Activities. The EDAQ was originally developed and partially tested in the mid-1990's with women with rheumatoid arthritis in Sweden[32,33] and translated into English by Beaton et al, 2000. It has been psychometrically tested several conditions including chronic pain[34].

PROMIS-29 v2.0 profile[30]: The PROMIS-29 v2.0 profile measure assesses pain intensity using a single 0–10 numeric rating item and seven health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance) using four items for each domain. PROMIS-29 has an excellent test-retest validity (≥0.80)[26]

EQ-5D-5L[36]: The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement. EQ-5D-5L exhibits excellent psychometric properties across a broad range of populations, conditions and settings[37].

Furthermore, CRPS participants will undergo a clinical test to measure their tactile acuity, the two-point discrimination threshold (2PD[38]), which will be assessed at the

pulp of the index finger or hallux (depending on the CRPS location, taking approximately 5 minutes) to all CRPS patients included.

Two point discrimination threshold at the pulp of the index finger or hallux: As a measure of tactile acuity, a two point discrimination test will be undertaken on the distal pulp of the index fingers (IF) of both the affected and unaffected hands (both IFs in HVs) according to Moberg's method (1990)[38]. This test assesses the smallest distance at which an individual can clearly distinguish between two points applied simultaneously to the skin. With the participant's eyes closed, the aesthesiometer (Homecraft Rolyan, Nottingham, UK) is applied to the surface with the smallest possible distance between the two points until the skin blanches. The participant reports whether they feel the touch of one or two points. The distance between the two points is gradually increased for each trial until the participant correctly discerns two rather than one point. Three consecutive correct answers at the smallest discernable distance determine the two-point discrimination threshold (2ptDT). We will perform three 2ptDT assessments over the course of the intervention (i.e. at baseline, half way through the intervention, and immediately after the intervention). Sham trials involving stimulation of one point only will be pseudo-randomly included, with a total of 1-4 sham trials per 2ptDT assessment. Three threshold measurement trials will be taken on the index finger of each hand during each 2ptDT assessment. The mean of these trials will be calculated for each IF. The estimated completion time for each 2ptDT assessment is 5 minutes. Patients' two-point discrimination will be assessed using this tool twice in total – once at the beginning of session 2 and once at the end of session 3.

- *Training for treatment partner*: in additional to the outcome measures, MPB will individually clinically assess each CRPS patient participant including but not limited to:
    - Pain assessment: Pain intensity, pain location, pain triggers, pain beliefs/attitudes, presence of sensory symptoms (such as allodynia and/or hypersensitivity).
    - Posture (standing / sitting, postural shift).

- Functional strategies (including posture, transfers and ADLs): Inability/struggle to perform certain tasks involving the painful limb (e.g. gait or reach-to-grasp).
- Current mobility / falls history / risk of falls.
- Movement (range, strength, quality, weakness, motor dysfunction).
- Significant Dysfunction (e.g. BPD, allodynia, hypersensitivity, dystonia, hypervigilance, inattention, relationship with affected body part (e.g. attention, feelings, associations, perception, representation, amputation desire)
- Secondary Issues (e.g. non-CRPS symptoms, incontinence).

Based on each clinical presentation, MPB will produce an individualized CMR treatment for each CRPS participant: This treatment plan will consist on 2-5 CMR tasks that the treatment partner will deliver to CRPS participant during the intervention phase. A hard copy of every task will be handed to the treatment partner (an example can be found in the Appendix section 1). For every single CMR tasks the follow information will be given:

- Task number.
- Task name.
- Task description.
- Material required (e.g. different fabrics).
- Patient position.
- Modality includes a step-by-step procedure to deliver the task.
- Number of repetitions:
- Photos:

As a part of session 1, treatment partner will observe and learn the treatment plan under the supervision of MPB (i.e. practising the exercises with MPB's guidance). The training session will end when treatment partner will be competent enough to deliver the intervention to good quality standards (will be assessed using the CMR tasks structure; cognitive problem (treatment partner is able to ask the question that

prompts the sensory discrimination - perceptual hypothesis (the CRPS participants is aware of which sensory information they have to focus on (e.g. tactile or proprioception) and verification (the treatment partner prompts the CRPS participants to check if they answer correctly). In case the treatment partner does not gain enough competency to deliver the intervention, further training will be offered from the lead investigator. A short questionnaire will be used to assess understanding and competency regarding the study intervention. Treatment partner will receive a hard copy with written guidance of the CMR tasks to be delivered including delivery instructions (an example can be found in the Appendix section 1).

There will be opportunities for both the CRPS patient and treatment partner to ask questions regarding CMR. The overall goal of this session is to prepare both CRPS patients and treatments partner to engage with the CMR treatment.

The anticipated total duration of session 2 is up to 3 hours with a rest break within the session.

Intervention phase:

The CMR home-intervention involves the recommended treatment plan being delivered by the treatment partner over a four-week period. The CRPS patient and treatment partner can refer to the written guidance provided for the different recommended tasks (an example can be found in the Appendix section 1). As part of a feasibility study the CRPS-patient and treatment partner would have agreed with MPB about the duration and frequency of the intervention sessions and this will be recorded in the written treatment plan. MPB will encourage treatment partner to deliver the intervention daily. A rehabilitation diary will be provided to record frequency and duration of treatment sessions and any other comments (see Appendix 2 for an example).

Weekly Zoom meetings will be agreed between the CRPS-participant, treatment partner, MPB and Marco Rigoni (Cognitive Multisensory Rehabilitation Centre, Italy) in order to evaluate progress on the intervention and modify treatment plan if required (e.g. increasing the complexity of the tasks or adding new CMR tasks). Marco Rigoni who will supervise the CMR treatment during the weekly zoom calls, providing further specialist CMR knowledge.

Session 2: Post-intervention clinical assessments

Following the four-week home-delivered intervention, CRPS patients and treatment partner will be invited to undergo the post-intervention clinical assessment session at the RUH in Bath. Post-intervention clinical assessments includes a repeat data collection of the self-reported measures completed at session 1 (see section Session 1).

Furthermore, CRPS-patients and treatment partner will be invited to attend an interview by MPB in order to gain insight in their experience of delivering/receiving CMR. The interview questions will be devised in order to gain insights on adherence, efficiency, acceptability, and safety of the intervention. This interview will include the discussion of:

- Content,
- Goals,
- Duration,
- Frequency and
- Modality of delivery of CMR

The anticipated total duration of session 1 is up to 1 hour.

3.4 Analysis

Planned analyses specific to each study aim:

1. **To identify the suitability, feasibility of delivering CMR in people with CRPS**. In order to answer the overarching research question the total number of sessions, their duration and frequency will be described as well as the presence of any exacerbation of symptoms during the intervention will be recorded rehabilitation diary, which will be handed to the lead investigator during session 2.

Furthermore, descriptive comments regarding both delivering and receiving the intervention will be collected on the interview sessions, goals, duration, frequency and modality of delivery of CMR. The diary will be analysed in order to gain insight on the adherence, efficiency, acceptability, and safety of the intervention.

2. **To determine the feasibility of running an appropriately powered efficacy study on the effectiveness of CMR in CRPS**. In order to gain some

preliminary insights into the potential effectiveness of the intervention, we will inspect for each person the change in scores on each outcome measure, relative to clinically meaningful differences. Pre- and Post-intervention clinical assessments data will be described and summarized, and their distribution will be ascertained using IBM SPSS Statistics (SPSS Inc, Chicago USA).

4. Research procedure risks and benefits

4.1 Anticipated risks

The potential risk for our patient participants is a temporary exacerbation of pain/discomfort, or nausea/dizziness related to the altered perception of their affected limb. These temporary changes should all settle within 24 hours after testing or the intervention. In the unlikely event that these effects persist for more than 48 hours, the participant will be advised to consult with their GP.

Procedures for recording incidents or adverse events

In the unlikely event that the participant experiences an adverse or unanticipated effect, they will be encouraged to contact the principal investigator (MPB) by phone or email who will provide advice. All symptoms and adverse events reported will be collected by the researchers and added to the participants' files. Both adverse effects related to the study (i.e. they resulted from the intervention administration or of any of the research procedures) and unexpected (i.e. not listed in the protocol as an expected occurrence) will be emailed to the research ethics committee (REC) within three days.

4.2 Anticipated benefits

We anticipate that there might be benefits in participating in the study. These include improvements in pain, limb spatial awareness, tactile acuity, body perception disturbances and physical function. Furthermore, we hope that by evaluating the feasibility of this intervention, we can develop future non-invasive treatment alternatives that can target CRPS-related signs and symptoms.

5. Ethical and legal considerations

5.1 Ethics

Prior to the commencement of this research study an application and the study protocol will be submitted to a Research Ethics Committee (NRES) through the Integrated Research Application System (IRAS) with the South West Committee.

All patients will continue to receive their routine care as appropriate and any voluntary involvement in this study will be in addition to that care. Participants will be informed that their participation is voluntary and that they can terminate the study at any time if they wish to do so without any consequences for their routine care.

Research data security, management and storage

The study will comply with the GDPR rules and the Data Protection Act. The term research data in this protocol refers to all forms including and not restricted to video recordings, paper and digital data.

Paper consent forms signed to indicate the voluntary participation in the research study will be stored securely only at the Royal United Hospital in Bath. Personally identifiable data (such as contact details, subjects' name, NHS number or date of birth) and data collected from the study will be anonymized and allocate unique identifier and then kept within a digital data file, securely stored on a password protected and encrypted shared drive at the RUH in Bath; this shared drive can be remotely accessed from secure computers at the University of West of England and Bath by Jenny Lewis. The research team may look at the participants' medical history subjects' suitability for the study.

Once the study is completed and the personally identifiable data are no longer needed the file containing personally identifiable data will be deleted according to the RUH guidelines.

If the participant stop being part of a research study at any time, the research team will keep the research data about you that they already have.

Encoded descriptive and psychometric participant data will be imported and analysed using data analysis software, e.g. SPSS. These electronic files will be stored within the encrypted study network at the RUH, which is accessible only via password protected computers, and on a password protected and encrypted shared drive at UWE and UoB; the last two can be remotely accessed from secure computers at the UoB by Janet Bultitude and by Dr Jenny Lewis at UWE.

Data management plan

While only MPB will have access to personally identifiable data, all named researchers will have access to the data once anonymised and encoded. The responsibilities of the data management and its analysis are listed in the following table (see table). Please note that Janet Bultitude will assist in the analysis.

Data archiving

As per NHS Research Ethics Committees, paper and digital data will be stored at Royal United Hospital and kept 5 years.

Complaints

If a participant complains about how researchers have handled your information, they will need to contact the research lead, MPB. If they do not receive a satisfactory response, they will be pointed to contact the Data Protection Officer.
Information Commissioner's Office (ICO) (www.ico.org.uk or 0303 123 1113).

Data management plan

While only MPB will have access to personally identifiable data, all named researchers will have access to the data once anonymised and encoded. The responsibilities of the data management and its analysis are listed in the following table.

Table 1 Data management plan

	Marc Aureli Pique Batalla	Jenny Lewis	Janet Bultitude	Marco Rigoni
Obtaining study consent and storing consent forms	☑			
Collecting and storing demographic and psychometric data	☑			
Encoding data (allocating participant code)	☑			
Baseline clinical assessment and treatment prescription	☑			
Follow up CMR treatment	☑			☑
Collecting data post-intervention	☑			
Transferring data to statistic program, e.g. SPSS	☑			
Data interpretation	☑	☑	☑	☑
Discussion of the data for publication/dissemination	☑	☑	☑	☑
Write manuscript for publication in peer-reviewed journal	☑	☑	☑	☑
Agree on final manuscript draft before submission	☑	☑	☑	☑

6. Participant expenses

All reasonable participant travel and parking costs to attend research visits to Bath will be reimbursed. Funding has been secured from Royal National Hospital for Rheumatic Diseases Donated Research Funds.

7. Publication and dissemination.

Findings from this study will be written up for publication in appropriate peer-reviewed academic journals. No patient identifiable data will be used. Furthermore, these findings will be disseminated both in written and oral forms at relevant national and international conferences.

8. Scientific and statistical review

The proposed study has been scientifically peer reviewed as part of the Royal National Hospital for Rheumatic Diseases Donated Research Funds award process.

Statistical analysis will be conducted using IBM SPSS Statistics 23 (SPSS Inc, Chicago USA) and will be supervised by Janet Bultitude (University of Bath).

9. Research sites and investigators

Research data collection will be undertaken at RUH in Bath by MPB (session 1 and 2). Treatment will be determined by MPB and supervised by MPB and Marco Rigoni (Cognitive Multisensory Rehabilitation Centre, Italy). Data analysis will be undertaken at RUH in Bath.

10. Research costs

Award funding from a Royal National Hospital for Rheumatic Diseases Donated Research Funds grant covers the research costs for this study.

11. Proposed time frame

Month

0-2: Ethics

2-4: Identification of potential participants and recruitment

6-10: Data collection

10-12: Data analysis and dissemination

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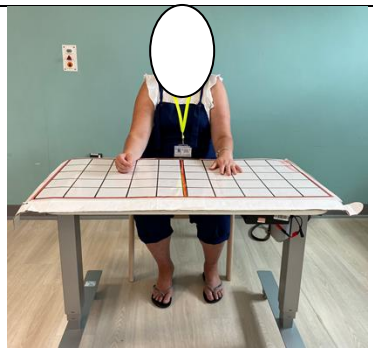
Appendix 1: Example of CMR task sheet for treatment partner

Task number:	1
Task name:	Spatial discrimination and comparison between affected and unaffected arms.
Task description	In this exercise the therapist positions the patient's unaffected hand in a grid position and asks the patient to position her affected hand in the same positioning the opposite grid to 'mirror' the unaffected hand.
Material required	A table, and table grid (optional)
Patient position	Comfortable sitting position in a chair both arms resting in a table.
Modality	Patient with eyes closed. Therapist to move patients' unaffected arm into a position. Patient prompted to match (i.e. to mirror) the position with affected arm paying attention to the position on the arm rather than pain. Encouraged patient to verify by opening eyes.
Number of repetitions	___ repetitions
Photos	 

Appendix 2: Example of rehabilitation diary for the home-based intervention

Please insert date and total duration of the session:				
Task number:				
Able to complete?	Yes	No, provide the reason:		
Total time task (in minutes) and number of repetitions	___min.	__repetitions		
Patient was able to answer correctly	Yes, always	Yes, often	Yes, sometimes	Not at all
Any adverse effects (including symptom flare)	Yes, please describe	No		
Task number:				
Able to complete?	Yes	No, provide the reason:		
Total time task (in minutes) and number of repetitions	___min.	__repetitions		
Patient was able to answer correctly	Yes, always	Yes, often	Yes, sometimes	Not at all
Any adverse effects (including symptom flare)	Yes, please describe	No		

Appendix 3: Participant consent form

PARTICIPANT CONSENT FORM A: CRPS PATIENT

COGNITIVE MULTISENSORY REHABILITATION, A NOVEL SENSORIMOTOR INTERVENTION FOR PAIN REDUCTION IN COMPLEX REGIONAL PAIN SYNDROME: A FEASIBILITY STUDY

Name of researcher: Marc Aureli Pique Batalla

Please initial **either** the YES **or** NO box

		YES	NO
1.	I confirm that I have read and understood the information sheet dated [20/07/2023, V5] for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. There will be 3 copies of this document: x1 copy for participant, x1 copy for medical records and x1 copy for investigator's site file.	☐	☐
2.	I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care and legal rights being affected. I understand that data collected prior to my withdrawal will be used in the study.	☐	☐
3.	I understand that researchers from the Royal United Hospital (RUH; Marc Aureli Pique Batalla and Jenny Lewis), University of the West of England (UWE; Jenny Lewis), University of Bath (UoB; Janet Bultitude) and Cognitive Multisensory Rehabilitation Centre (Marco Rigoni) that are part of this study may examine and analyse data collected during the study. I give permission for these individuals to have access to this anonymised data.	☐	☐
4.	I understand that all information and data collected from me, as part of the project will be securely retained by RUH for 5 years in line with NHS National record management guidelines.	☐	☐
5.	I consent to be audio recorded.	☐	☐
6.	I confirm that my data, which will be anonymized, can be used for future undescribed analyses by researchers who may, but are not necessarily members of the named team of researchers responsible for the current study	☐	☐
7.	I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from University of the West of England (UWE; Jenny Lewis), University of Bath (UoB; Janet Bultitude) and Cognitive Multisensory Rehabilitation Centre (Marco Rigoni), from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records	☐	☐
8.	I agree to take part in the above study.	☐	☐

Data protection

The Royal United Hospital (RUH) will process your data in accordance with the General Data Protection Regulation as applied, enacted and amended in UK law. Your data will only be processed with your consent for the purposes described above and will only be shared outside of Royal United Hospital (including overseas with appropriate safeguards) in the circumstances described above.

Your rights

In respect of your personal data held by us, you have the following qualified rights to:

- access it
- receive it in a structured machine readable format
- rectify it if it is not accurate or complete
- erase it
- restrict its processing
- withdraw any consent provided or otherwise object to its processing
- complain to the Information Commissioner's Office (ICO)

To find out more or to exercise any of these rights please contact the Data Protection Officer via e-mail: dpo@ico.org.uk

……..

Name of patient Date Signature

……

Name of person taking consent Date Signature
(If different from researcher)

……..…….

Name of researcher Date Signature

Appendix 4: Recruitment packaged log

CRPS patient's name		Attended CRPS Initial Assessment (Y/N) If yes, please insert the date	Interested in participating? (Y/N)	Handed recruitment pack (Y?N) If yes, please insert the date		Attending CRPS rehabilitation program (Y/N)? If yes, please insert the date	Interested in participating? (Y/N)	Sent recruitment pack (Y/N) If yes, please insert the date