Final Report to RSDSA – August 2020

A Delphi study to define internationally agreed core clinical outcome measures for Complex Regional Pain Syndrome clinical research studies (COMPACT-C)

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Background

Complex Regional Pain Syndrome (CRPS) is a severe chronic pain condition, usually in a single limb, and characterised by a wide range of sensory, motor and autonomic abnormalities. The multidimensional nature of the condition means CRPS clinical trials have historically used a diverse range of outcome measures. This has hindered the meaningful comparison and pooling of data and has been a limiting factor in advancing our understanding of the condition[1]. In 2017, the COMPACT consortium published recommendations for a minimum core set of patient-reported outcome measures[2].

These initial recommendations subsequently led to the development of two complementary studies. COMPACT-Q is testing the feasibility and acceptability of using an electronic data capture system internationally to collect and manage the patient-reported questionnaire data. COMPACT-C has been using an electronic Delphi process to develop and achieve consensus on an accompanying set of internationally agreed clinical outcome measures. This report relates to the progress made to date with regards to COMPACT-C.

Methods

A systematic literature review identified 44 broad clinical outcome areas reported in CRPS clinical studies from 2000-2018. Consultation with clinicians and academics refined this to 59 specific clinical outcomes for potential inclusion in a minimum core set of clinical outcomes. CRPS clinicians and researchers were recruited to an e-Delphi study via email invitation from the IASP CRPS Special Interest Group and the International Research Consortium for CRPS.

In round 1 of the e-Delphi study, respondents rated each of the 59 outcomes on a 1-9 scale in relation to its relevance to the question: “What is the clinical presentation and course of CRPS, and what factors influence it?” (1=not relevant, 9=highly relevant). Free text comments were also invited. In round 2, respondents were presented with their individual ratings, the median group

ratings for each outcome, and anonymised free-text comments. They re-rated each outcome in the light of this information. Consensus was considered achieved for each outcome that had a final group median score of ≥ 7, as agreed by 75% of respondents[3]. The feasibility and practicability of collecting these clinical data were then considered by members of the COMPACT consortium.

Results

Sixty participants, representing 21 countries, completed both rounds 1 and 2 of the e-Delphi survey. Outcomes meeting the consensus criterion were:

- record of diagnosed psychological co-morbidities
- degree and extent of brush-evoked allodynia and hyperalgesia
- level of activity (as determined by wearable devices)
- name and dosage of current medication
- clinical assessments of anxiety and depression
- clinical assessment of Post-Traumatic Stress Disorder
- quantitative assessment of skin temperature

Post-study consultation with members of the COMPACT consortium assessed the feasibility and acceptability of each of these outcomes for use in clinical setting. From this it was agreed that the final data set should include a record of medication as a core clinical outcome; with two further optional (non-core) clinical outcomes relating to the mapping of allodynia and the recording of skin temperature. Protocols are currently being finalised for these outcomes. Please see Appendix A for examples of proposed data collection screens for these clinical data plus a draft protocol for the use of infra-red temperature assessment of skin temperature. It was also proposed to that a standardised patient-reported measure of PTSD should be added to the existing COMPACT patient-reported core measurement set .

Psychological co-morbidities and level of activity were determined impractical to measure consistently across all CRPS study centres. Hyperalgesia, depression and anxiety were considered already sufficiently captured within the COMPACT patient-reported core measurement set.

Conclusion

Findings from the COMPACT-C study have been discussed with the international CRPS community and work is now underway to finalise the data collection protocol for the core and optional clinical outcome measures. A manuscript presenting our findings is in preparation.

The associated feasibility study to test the acceptability of using an electronic data management system to capture the patient-reported outcomes (COMPACT-Q) will conclude by early 2021. This system will also be used for the management of the COMPACT-C data. This will enable the final combined set of COMPACT patient-reported and clinical outcome measures to be incorporated into the full development of an international registry and to be advocated for use in all future CRPS clinical studies.

Acknowledgements and thanks

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professional members of the COMPACT consortium, and the clinicians and academics from the CRPS community who kindly participated in this study.

References

[1]Grieve S, Jones L, Walsh N and McCabe C, 2016. What outcome measures are commonly used for Complex Regional Pain Syndrome clinical trials? A systematic review of the literature. *European Journal of Pain*, *20*(3), pp.331-340

[2]Grieve S, Perez R.S, Birklein F, Brunner F, Bruehl S, Harden N, Packham T, Gobeil F, Haigh R, Holly J and Terkelsen A, 2017. Recommendations for a first Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies (COMPACT). *Pain*, *158*(6), p.1083

[3]McMillan S.S, King M, Tully M.P, 2016. How to use the Nominal Group and Delphi techniques. *International Journal of Clinical Pharmacy*, *38*(3), pp.655–662

Meetings held for research team

1. **1st June 2017 – Mainz, Germany (hosted by co-applicant Professor Frank Birklein).** Preparatory discussions conducted with international clinical academics, in order to begin identifying a clinical outcome measurement set. *Please note: this work took place prior to the submission of the study funding application to the RSDSA*
2. **12th September 2018 – Boston, USA (coinciding with the IASP World Congress on Pain).** First workshop for clinicians and academics within the COMPACT consortium. Data from this workshop informed the list that comprised the first round of the e-Delphi survey
3. **12th February 2019 – teleconference meeting with the project management group.** Outstanding queries in relation to the first round of the e-Delphi survey were discussed. Methods and distribution timeframe for both rounds of the survey were agreed
4. **4th September 2019 – Valencia, Spain (coinciding with EFIC European Pain Congress)**. Second workshop for clinicians and academics within the COMPACT consortium. Presentation of the e-Delphi survey results were followed by discussion. Group consensus was obtained regarding the measures that should be included as core and optional clinical outcomes
5. **15th April 2020 – teleconference meeting with the project management group**. Outstanding queries in relation to the draft core clinical measurement set were discussed and actions for further progress agreed. A written update relating to the agreed action points was disseminated to project group members via email in August 2020 and feedback requested in order to finalise the protocols for the recording of the agreed clinical outcome data.

Dissemination activities to date

- **5th April 2019 – Bristol, UK. Poster and oral presentation of the study protocol.** The study was presented in both formats at the Centre for Health and Clinical Research Showcase Conference, University of the West of England.
- **March 2020 - IASP World Congress on Pain.** An abstract presenting the e-Delphi survey results was accepted for presentation in Amsterdam, Netherlands, August 2020. Unfortunately this has been postponed until **June 2021** due to the Covid-19 pandemic.

- A commentary article presenting study outcomes is currently being prepared for consideration by the journal Pain Medicine.

Finances

RSDSA Grant Income *(outstanding monies are listed in italics):*

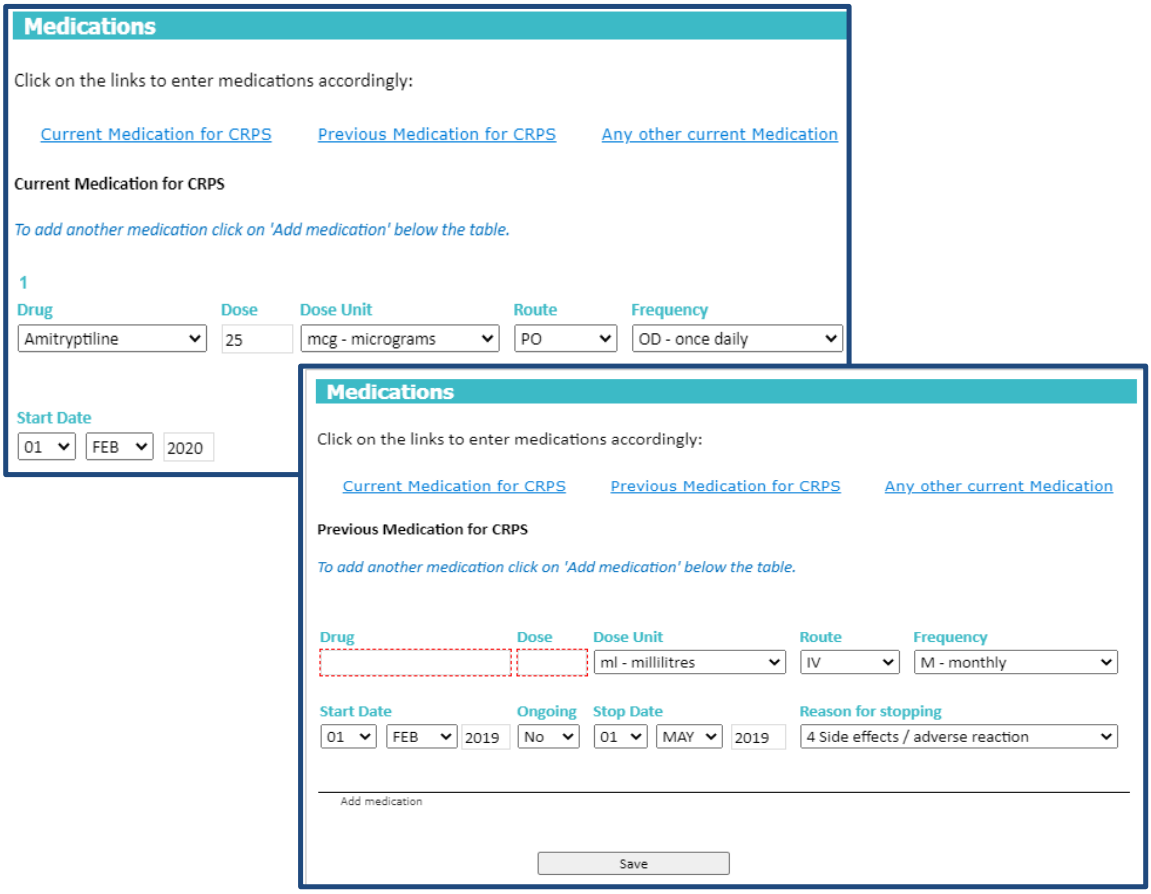
October 2018	First instalment	$32,462.50
July 2019	Second instalment	$32,462.50
September 2019	Third instalment	$32,462.50
November 2019	Fourth instalment	$19,477.50
Pending study completion	*Final 10%*	*$12,985.00*
Total value of grant		**$129,850.00**

Study Expenditure *(outstanding expenses are listed in italics):*

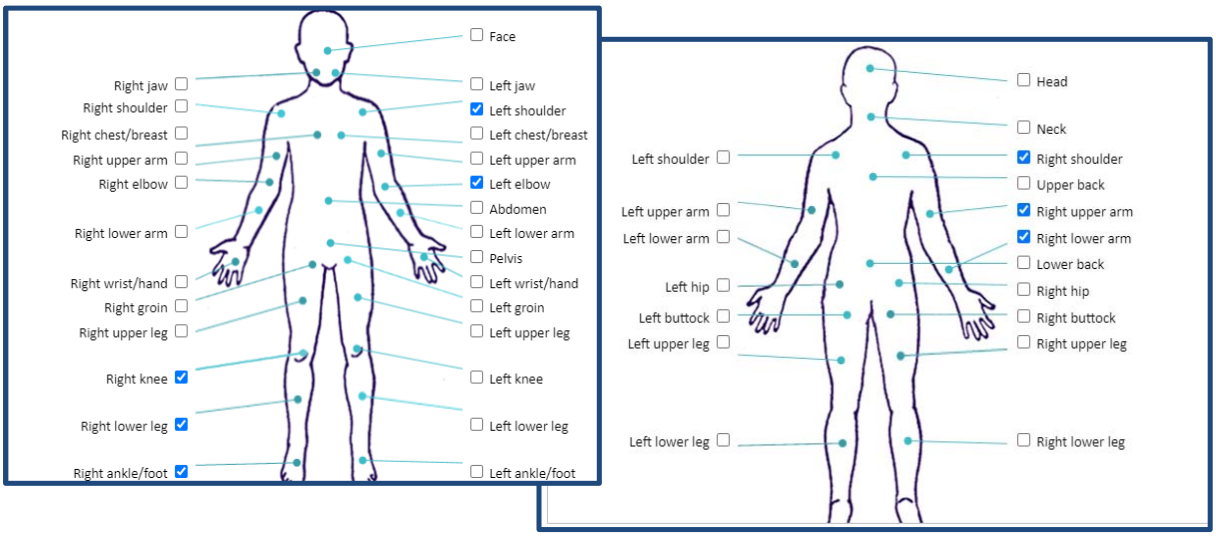
Salary costs for 26 months , which includes conduct of the study, dissemination of study findings and integration of findings into ALEA database and Core data set	Chief Investigator, Study Co-ordinator, Study Administrator	$90,500.00
Project management costs	Teleconference meetings, ISRCTN Registry fee	$1,500.00
Workshop 1 costs	Boston travel, accommodation and subsistence	$4,665.00
Workshop 2 costs	Valencia travel, accommodation and catering fees	$2,468.00
Project management costs	*Contribution to IRC, translation costs*	*$7,100.00*
IT costs	*ALEA development, hosting and data storage*	*$14,600.00*
Dissemination costs	*International conference attendance, poster presentation fees, final discussions to agree how the findings will be integrated into the international registry*	*$8,500.00*
Total Expenditure		**$128,929.00**

Appendix A: Draft clinical outcome data collection

Proposed medication record



Proposed allodynia body map



COMPACT-C: thermal assessment recommendations[1]

RECOMMENDED ASSESSMENT PROCEDURE

1. Wherever possible, conduct thermal assessments at the end of a consultation, this allows time for acclimatisation to have taken place.

2. Identify the limb where the patient reports worst pain, and assess the area on/nearest the point of worst pain.

3. Identify the optimum measurement distance for the area being assessed (see Distance to Spot Ratio information below).

4. So as to give meaningful comparison when comparing left/right, IR spot measurements should be acquired from the same distance and perpendicular to the skin surface on each limb.

5. Ensure the areas being assessed are free from obstruction (clothes, lidocaine pads etc.) The temperature measurement is a function of the material it is being pointed at. Tattoos will not affect measurements.

6. Avoid completing temperature assessments with a patient positioned in direct sunlight. Whilst skin lends itself well to IR temperature assessment, to ensure the measurement does not pick up extraneous IR, conducting assessment in a shaded room, or one lit evenly with standard overhead lighting, will improve accuracy.

7. If possible keep the IR thermometer at room temperature within the room that it is to be used. The thermometer algorithm works on measuring ambient temperature and therefore a 'cold start' should be avoided. It is recommended that the device is left on charge for at least 15min before use.

8. Keep the thermometer lens clean and dry, using the lens cap, if provided.

Distance to Spot Ratio

- Within the specification of an IR spot thermometer, there should be a 'distance to spot value' (D:R). This is an approximate ratio between the distance between the IR sensors and the sensing surface to the diameter of the spot size being assessed.
  - Cheaper devices can have ratios close to 1:1 (large spot). Higher specification devices can have a ratio of 60:1 (small spot). The Flir TG165 tested in preparing these recommendations has a reported D:R of 24:1.
- D:R values should also be considered when taking measurements to ensure these are not taken from too great a distance i.e. if assessing a 4cm wrist with a device with a ratio of 24:1, the IR spot thermometer has to be at least within 1m otherwise the spot sensing area would be too big and will start to take in the background temperature also.
- All assessments should also follow the device's stated 'minimum measurement distance (e.g. the Flir TG165 has a minimum distance of 254mm (10mm diameter spot)).

[1] Informed by testing of Flir TG165 device by Clinical Imaging & Measurement, Medical Physics & Bioengineering Department, Royal United Hospitals Bath, UK,