IMPROVING HEALTH OUTCOMES IN COMPLEX REGIONAL PAIN SYNDROME TO INFORM CHRONIC PAIN PRACTICE

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Published work and a critical commentary submitted in partial fulfilment of the requirements of the University of the West of England, Bristol for the degree of Doctor of Philosophy by publication (DPhil)

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DECLARATION OF AUTHORSHIP

I can confirm that none of the presented publications for the award of Doctor of Philosophy (DPhil) have been submitted for another academic award either in this or any other institution.

I can confirm that all of the work presented in this doctoral thesis, including the presented publications and accompanying commentary, is the original work of the author.

I confirm that I have met the necessary training requirements of 60 credits at M level.

Table 1.1 lists my personal contribution to the publications in this thesis.

Statement confirming that this work has not been submitted for another academic award

I can confirm that none of the selected publications for the award of Doctor of Philosophy (DPhil) have been submitted for another academic award either in this or any other institution.

ABSTRACT

The research presented in this thesis focuses on improving health outcomes in the field of complex regional pain syndrome (CRPS) to inform chronic pain practice. Eight publications are presented, each accompanied by a critical commentary to evidence my contribution to the creation and interpretation of new knowledge in this field. The Researcher Development Framework (Vitae, 2010) provides a thread of connectivity against which my professional and personal development is mapped and evidenced.

Several key research findings are presented in these publications. People with CRPS currently lack the information they need to self-manage their condition and healthcare professionals have difficulty diagnosing CRPS and using published diagnostic criteria. This may result in misdiagnosis and inappropriate management of CRPS, which may have long-term consequences for the patient in relation to receiving appropriate and targeted treatments. Future research should assess the impact of recently published CRPS European Standards in terms of uptake and impact on CRPS clinical practice.

The research findings also reported a novel method of communicating and representing changes in body perception disturbance using digital media. This directly impacted CRPS clinical care as it allowed individuals to depict an alteration in body perception more accurately than relying on their verbal articulation of the changes. Future modifications should focus on developing technology for independent patient use which would mitigate the need for health professionals to administer the tool, promote patient self-management and provide scope for the technology to be used in a home-setting.

Research found that the presence of pain lowers the threshold for the detection of sensorimotor disturbances, and this is strongly related to the intensity of pre-existing pain. It was found that the higher the level of pre-existing pain, the greater the report of sensory and motor disturbances. This confirms the benefit of routinely used clinical interventions that seek to improve sensorimotor congruence. Future research should investigate whether this mechanism contributes to the *maintenance* of pain in clinical populations.

Three publications contributed to an ongoing, iterative programme of research which will inform the development of an international CRPS clinical research

registry. The first questionnaire core outcome measurement set for CRPS clinical studies was agreed and recommendations were made for the collection of standardised CRPS outcome data. For the first time, an international CRPS registry will provide access to a large data set of CRPS-specific outcomes for interrogation. In the long-term, this has the potential to improve health outcomes for the CRPS population worldwide. It will enable researchers to better understand the potential phenotypes of CRPS and prognostic indicators, which in turn may impact clinical care through the development of more targeted therapeutic approaches.

My academic and clinical competence as an independent nurse researcher and a research nurse leader is demonstrated though my achievement of the 12 RDF sub-domains (Vitae, 2010). The clinical impact of my research is described, and recommendations are made for future research and clinical practice.

ACRONYMS

ALP	Advanced Leadership Programme
BPD	Body perception disturbance
BPT	Body perception tool
CIRU	Clinical Informatics Research Unit
COMPACT	Core Outcome Measures for complex regional PAin syndrome Clinical Trials.
COMS	Core outcome measurement set
CRN	Clinical Research Nurse
CRPS	Complex Regional Pain Syndrome
CS	Central sensitisation
CSS	CRPS Severity Score
EDMS	Electronic data management system
FMS	Fibromyalgia
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
IF	Impact Factor
IRC	International Research Consortium
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
MDL	Model of Domain Learning
MRes	Masters in Clinical Research
PCA	Principal component analysis
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and public involvement
PROM	Patient Reported Outcome Measure
QST	Quantitative Sensory Testing
RA	Rheumatoid Arthritis
REC	Research Ethics Committee
RDF	Research Development Framework
RUH	Royal United Hospitals Bath NHS Foundation Trust
UK	United Kingdom
UWE	University of the West of England
VF	Visual feedback
WHO	World Health Organisation
WHO ICD-11	World Health Organisation International Classification of Diseases 11th Revision

Table 1.1: Personal contribution to the publications included in this thesis

N°	Publication	Publication and Impact Factor (IF)	My contribution
1	McCabe, C., Gauntlett-Gilbert, J., **Grieve, S.,** Lewis, J. and Walsh, N. (2018) **Multi-disciplinary Approaches to Managing Long-term Pain in Arthritis.**	In: ***Rheumatology*** Hochberg *et al.* (2018) *7th Edition.* Elsevier: Philadelphia**,** pp.434-438	**Book chapter:** • Wrote specific sections of this chapter in relation to outcome measures and patient education • Contributed to the chapter as a whole to ensure my contributions were situated appropriately within the entire text • Reviewed the proof and made corrections
2	Turton, A., Palmer, M., **Grieve, S.,** Moss, T., Lewis, J. and McCabe, C. (2013) **Evaluation of a prototype tool for communicating body perception disturbances in complex regional pain syndrome.**	**Frontiers in Human Neuroscience.** 7 (517), pp.1-8 IF:2.871	**Study:** • Delivered the study in an NHS setting • Co-designed the standardised questionnaire • Contributed to the ethical approvals process • Conducted the informed consent process • Recruited the study participants • Collected data using the digital tool and administered the standardised questionnaire • Contributed to the qualitative data analysis **Paper:** • Reviewed the peer reviewed manuscript prior to submission
3	Brun, C., Mercier, C., **Grieve, S.,** Palmer, S., Bailey, J. and McCabe, CS. (2018b) **Sensory disturbances induced by sensorimotor conflicts are higher in complex regional pain syndrome and fibromyalgia compared to arthritis**	**European Journal of Pain.** 23(3), pp.483–494 IF: 3.188	**Study:** • Contributed to the quantitative analysis strategy and the interpretation of the findings **Paper:** • Wrote the methodology section and commented on the overall manuscript • Responded to the reviewers' comments regarding the methodology

	and healthy people, and positively relate to pain intensity.		
4	**Grieve, S.,** Adams, J. and McCabe, C. (2016a) **"What I really needed was the truth". Exploring the information needs of people with CRPS.**	**Musculoskeletal Care**. 14(1), pp.15-25. IF:1.92	**Study:** • Principal Investigator, responsible for overall study design, delivery and management • Designed the protocol and study documents (consent, PIS etc.) • Responsible for ethics application, submission and amendments • Received Informed consent from participants • Conducted study recruitment • Organised and conducted the interviews • Typed the transcripts and analysed qualitative data • Presented findings at conferences as poster and an oral presentation **Paper:** • First author • Wrote first draft and subsequent drafts • Submitted paper and responded to reviewers' comments
5	**Grieve, S.,** Jones, L., Walsh, N. and McCabe, C. (2016b) **What outcome measures are commonly used for Complex Regional Pain Syndrome clinical trials? A systematic review of the literature.**	**European Journal of Pain.** 20, pp.331–340. IF: 3.188	**Study:** • Designed the research question and protocol • Defined the search strategy • Conducted the systematic literature review • Led data analysis • Reviewed a subset of the data with a co-researcher at a later stage of the data analysis due to volume of results • Presented poster at national conference • Oral presentation at an international meeting of CRPS experts **Paper:** • First author • Wrote first draft and revised subsequent drafts • Submitted paper and responded to reviewers' comments, resubmitted

6	**Grieve, S.,** Perez, R.S.G.M., Birklein, F., Brunner, F., Bruehl, S., Harden, R.N., Packham, T., Gobeil, F., Haigh, R., Holly, J., Terkelsen, A., Davies, L., Lewis, J., Thomassen, I., Connett, R., Worth., T, Vatine, J-J. and McCabe, C.S. (2017c) **Recommendations for a first Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies (COMPACT).**	**Pain** 158(6), pp.1083-1090. IF: 6.029	**Study:** • Overall project co-lead • Contributed to study design • Reviewed the relevant literature • Co-ordinated and delivered this international project including liaison with international experts in the field of CRPS • Co-ordinated and co-chaired the international workshops • Prepared funding application • Oversight of study budget and timeline • Modelled potential core measurement sets • Co-led and contributed to the work defining and agreeing the CRPS questionnaire core measurement set • Sought approvals to use the defined outcome measures from the authors/distributors • Organised and led focus groups • Led patient involvement activities • Presented posters and oral session at national and international conferences **Paper:** • First author • Wrote first draft and revised subsequent drafts • Submitted paper and responded to reviewers' comments

7	**Grieve, S.,** Brunner, F., Buckle, L., Gobeil, F., Hirata, H., Iwasaki, N., Moseley, GL., Sousa, G., Vatine JJ., Vaughan-Spickers, N., Xu, J. and McCabe,C (2019a) **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.**	**Musculoskeletal Care.** 17(3), pp.249-256 IF:1.92	**Study** • Overall project co-lead • Co- designed the protocol • Identified an electronic data management system • Co-designed the research method • Compiled the full protocol • Obtained permission to use the questionnaire outcome measures within the protocol • Prepared funding applications • Registered the protocol **Paper:** • First author • Wrote first draft and edited feedback from co-authors • Submitted paper
8	**Grieve, S.,** Llewellyn, A., Jones, L., Manns, S., Glanville, V. and McCabe, C. (2019b) **Complex Regional Pain Syndrome: An international survey of clinical practice.**	**European Journal of Pain** 23(10), pp.1890-1903 IF: 3.188	**Study:** • Contributed to design of study and survey • Designed and wrote the protocol • Supervised the building of the survey using Qualtrics • Contributed to pilot testing • Undertook qualitative data analysis and contributed to quantitative data analysis. • Presented posters at national and international conferences **Paper:** • First author • Wrote first draft and revised subsequent drafts • Submitted paper

CHAPTER 1: INTRODUCTION

1.0. Overview of thesis

This thesis focuses on my research in the field of chronic pain, and specifically Complex Regional Pain Syndrome (CRPS). The research presented originates from my interest in improving health outcomes for this population and includes investigation into the mechanisms of chronic pain, the development of targeted treatments and the development of an international register to facilitate collaborative pain research.

The primary research presented is not intended to answer an overarching research question, however, the presented publications reflect a common aim throughout the research, which is to improve the health outcomes of an individual with chronic pain. The thesis therefore presents a cohesive body of work in which new knowledge on chronic pain is derived from a patient's perspective but also insight is gained into the experience of healthcare practice.

My research has been conducted over a seven-year period and during this time, as lead or co-author, I have contributed to ten published journal articles, one book chapter and eighteen published abstracts.

This thesis will present eight publications, listed in Table 1.2, each supported by a critical commentary (see full publications in Appendix 1). Six of the publications presented are primary research and reported the generation of new knowledge.

Table 1.2: Publications presented in this thesis

Nº	**Publication**
1	McCabe, C., Gauntlett-Gilbert, J., **Grieve, S**., Lewis, J. and Walsh, N. (2018) Multi-disciplinary Approaches to Managing Long-term Pain in Arthritis. In: Hochberg, M., Gravallese, E., Silman, A., Smolen, J., Weinblatt, M. and Weisman, M. (2018) *Rheumatology*. 7th Edition. Elsevier: Philadelphia, pp.434-438.
2	Turton, A., Palmer, M., **Grieve, S.,** Moss, T., Lewis, J. and McCabe, C. (2013) Evaluation of a prototype tool for communicating body perception disturbances in complex regional pain syndrome. *Frontiers in Human Neuroscience*. 7 (517), pp.1-8.

3	Brun, C., Mercier, C., **Grieve, S.,** Palmer, S., Bailey, J. and McCabe, C. (2018b) Sensory disturbances induced by sensorimotor conflicts are higher in complex regional pain syndrome and fibromyalgia compared to arthritis and healthy subjects, and positively relate to pain intensity*. European Journal of Pain.* 23(3), pp.483–494.
4	**Grieve, S.,** Adams, J. and McCabe, C. (2016a) “What I really needed was the truth". Exploring the information needs of people with CRPS. *Musculoskeletal Care*. 14(1), pp.15-25.
5	**Grieve, S**., Jones, L., Walsh, N. and McCabe, C. (2016b) What outcome measures are commonly used for Complex Regional Pain Syndrome clinical trials? A systematic review of the literature. *European Journal of Pain*. 20, pp.331–340.
6	**Grieve, S.,** Perez, R.S.G.M., Birklein, F., Brunner, F., Bruehl ,S., Harden, R.N., Packham, T., Gobeil, F., Haigh, R., Holly, J., Terkelsen, A., Davies, L., Lewis, J., Thomassen, I., Connett, R., Worth, T., Vatine, J-J. and McCabe, C. (2017c) Recommendations for a first Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies (COMPACT). *Pain.*158(6), pp.1083-1090.
7	**Grieve, S.,** Brunner, F., Buckle, L., Gobeil, F., Hirata, H., Iwasaki, N., Moseley, GL., Sousa, G., Vatine JJ., Vaughan-Spickers, N., Xu, J. and McCabe,C (2019a) 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. *Musculoskeletal Care*.17(3), pp.249-256.
8	**Grieve, S.,** Llewellyn, A., Jones, L., Manns, S., Glanville, V. and McCabe. (2019b) Complex Regional Pain Syndrome: An international survey of clinical practice. *European Journal of Pain*. 23(10), pp.1890–1903.

As the reader progresses though the publications and associated commentaries, it will be evident that I have a critical understanding of the current state of knowledge in the field of chronic pain and that I have contributed to the creation and interpretation of new knowledge through original research. My specific contribution to each publication will be described, to demonstrate my increasing academic and clinical competence as an independent researcher (Table 1.1, page xi).

The thesis is presented in four chapters.

The first chapter will introduce the value of using a professional development framework to underpin my thesis, specifically the VITAE Research Development Framework (RDF) (Vitae, 2010). I will describe how this was applied to demonstrate my personal and professional development as a researcher and it will be used to provide a thread of connectivity throughout the thesis. I will present my early development as a nurse researcher, and introduce my current research setting and professional role.

Chapter Two will critically appraise current literature in chronic pain and CRPS where relevant to this thesis. CRPS exhibits similar clinical manifestations as other rheumatology conditions and these will be described, in order to contextualise the potential broader relevance of my research.

Chapter Three will present the eight publications which comprise this thesis, each accompanied by a critical commentary of my individual contribution to the original research. Where new knowledge has been generated, this will be highlighted in the commentary and I will also describe my personal and professional development in relation to the publication and in the context of the RDF (Vitae, 2010).

Finally, Chapter Four will reflect on the different research philosophies used in the publications presented. The key findings addressed in this thesis will be discussed and will demonstrate how the research findings have contributed to greater understanding of the mechanisms and management of chronic pain, and specifically CRPS. Areas for future research will be identified. Reflections on undertaking this thesis will be shared and I will present how I intend to move forward, both as an independent nurse researcher and research nurse leader.

For the purpose of facilitating understanding of the content of this thesis, the term “health outcome” is defined as: those changes experienced or expressed by an individual that have arisen from receipt of a therapeutic healthcare intervention.

Ethical and institutional approvals have been obtained for the publications presenting primary research, where applicable. Throughout the thesis, ethical considerations will be discussed when I have made a notable contribution.

1.1. Overall aims of the DPhil thesis

1. To contribute new knowledge towards the improvement of health outcomes in the field of chronic pain and Complex Regional Pain Syndrome (CRPS), and to provide recommendations for future research and clinical practice.

2. To demonstrate my academic and clinical competence as an independent researcher.

1.2. Objectives:

1. To position my research within the context of published literature in chronic pain, and specifically CRPS.

2. To demonstrate how the original research presented in the selected publications has addressed identified gaps in the field of chronic pain and CRPS, and has contributed to the creation and application of new knowledge to improve health outcomes.

3. To demonstrate how I have applied my learning and decision making throughout my personal research journey, to begin to drive the research agenda by providing a focus for further investigation.

4. To evidence that I have met all twelve sub-domains of the VITAE Research Development Framework (Vitae 2010) and the UWE doctoral descriptors.

5. To recommend approaches for future research and clinical practice relevant to the publications presented.

1.3. A professional development framework

This section will introduce the concept and use of a professional development framework to underpin my thesis and the value of using this to support my published work presented in this thesis. The VITAE Research Development Framework (RDF) (Vitae 2010) will be described in detail.

1.3.1 Why select a framework?

My research interests centre upon chronic pain. The publications presented in this thesis include a range of research methodologies, study populations and topics under investigation within the field of chronic pain, and vary from experimental

research through to large datasets. Chronic pain is a broad topic area and, as with many journeys into the world of clinical research, I have pragmatically embraced opportunity and convenience, alongside my passion and dedication to my specific area of interest. The breadth of research within my published papers reflects this very varied journey and the multifaceted components of chronic pain research. The challenge was to recognise this variety and to provide a linking thread between these publications in order to demonstrate a coherent theme throughout the thesis (Smith 2015). Initially the options I considered to demonstrate connectivity were: (1) to link my publications in terms of my increasing competence as a researcher, from novice to expert; or (2) to categorise the publications into common topics or research methodologies. However, after critical reflection both options were rejected as, before undertaking the DPhil, I had already acquired many attributes and skills commensurate with an independent researcher and so did not consider myself a novice at the outset. In addition, my varied research journey encompassed a range of methodologies and did not lend itself to common topic areas within the field of chronic pain. I chose instead to use a professional development framework (PDF) as the thread of connectivity to underpin this thesis because it allowed me to take the reader through my journey to become an independent researcher by clearly mapping my development on to the framework.

As conceptual constructs, PDF's or professional development models (the terms are commonly used interchangeably), enable an individual to identify the knowledge, skills and attributes which are necessary for personal and professional growth (Keshmiri et al. 2019; Pena et al. 2010). I wanted to identify a framework, which would provide the overarching principles fundamental to my development as a researcher.

The process of selecting an appropriate framework was not easy and included a systematic review of the literature. Three frameworks were identified for consideration. The selection process is demonstrated in Table 1.3, p.6.

Table 1.3: Framework selection process

Selection Process	Author	Framework	Identification	Strengths	Limitation
1	Benner (1982)	Novice to expert stages of clinical competence	Prior knowledge of this model	• Well used within nursing literature. • Performance-focused	• Less emphasis on personal development (Carraccio *et al*. 2008) • Not comfortable with the term 'novice' as many years as a clinical research nurse and completion of MRes
2	Alexander (2003)	Model of domain Learning	Identified via systematic review of the literature	• Model for developing expertise in academic fields. • Three stages of expertise development which initially appeared to accurately conceptualise my professional journey; acclimation; competence; and proficiency or expertise.	• Strongly embedded in academia • An exercise to map my development on to this framework found it to be more applicable to educators than a clinical research environment
3	VITAE (2010)	Research Development Framework	UWE, Bristol web page for postgraduate researcher skills development[a]	• UWE promotes RDF as part of skills development for postgraduate researchers • Designed specifically as a professional development framework • Researchers can use it to identify their strengths and weaknesses and identify ways to fill the gaps • Comprises descriptors which represent the distinct stages of development as a researcher. • Prompts self-analysis of researcher's needs • Use is not prescriptive (Vitae, 2010) Adapted use is permissible	• Licensed for United Kingdom use only • Has been criticised for over -simplification (McGloin and Wright, 2013) • Does not specify actions, but rather prompts thinking

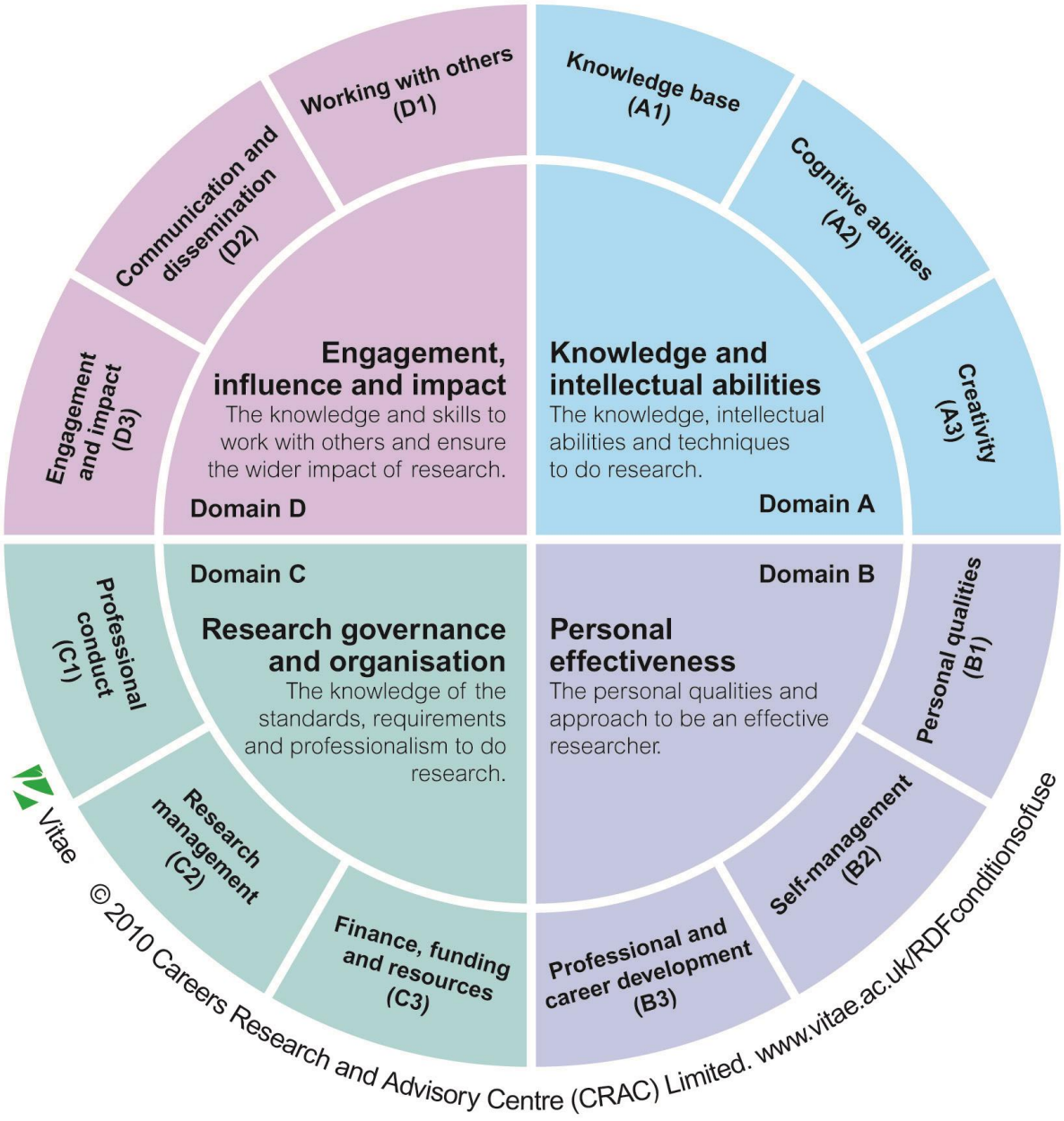
a https://www1.uwe.ac.uk/research/postgraduateresearchstudy/skillsdevelopment.aspx

From the selection process, it was clear that the Vitae RDF was the most robust tool to evidence my development as a researcher because, in demonstrating the attainment of the RDF competencies, the UWE doctoral descriptors are also achieved (Appendix 2). Utilisation of this framework is described in section 1.3.3.

1.3.2. The Vitae Researcher Development Framework (Vitae®, 2010)

The Vitae RDF was developed in the United Kingdom (UK) and describes the knowledge, skills, attributes and behaviours of successful researchers, to encourage them to attain their potential (Vitae, 2010). It therefore provides a framework to enable the researcher to plan, support and evaluate their professional and personal development. The RDF comprises 4 key domains and 12 sub-domains, with each sub-domain containing a number of descriptors which encompass "the knowledge, intellectual abilities, techniques and professional standards to do research, as well as the personal qualities, knowledge and skills to work with others and ensure the wider impact of research" (Vitae, 2010) (Figure 1.1). Throughout this thesis the 12 sub-domains will be referenced using the alphanumerical code listed in Figure 1.1, for example A1, A2 etc. The RDF is freely available for non-commercial use (Appendix 3).

Figure 1.1: VITAE Research Development Framework



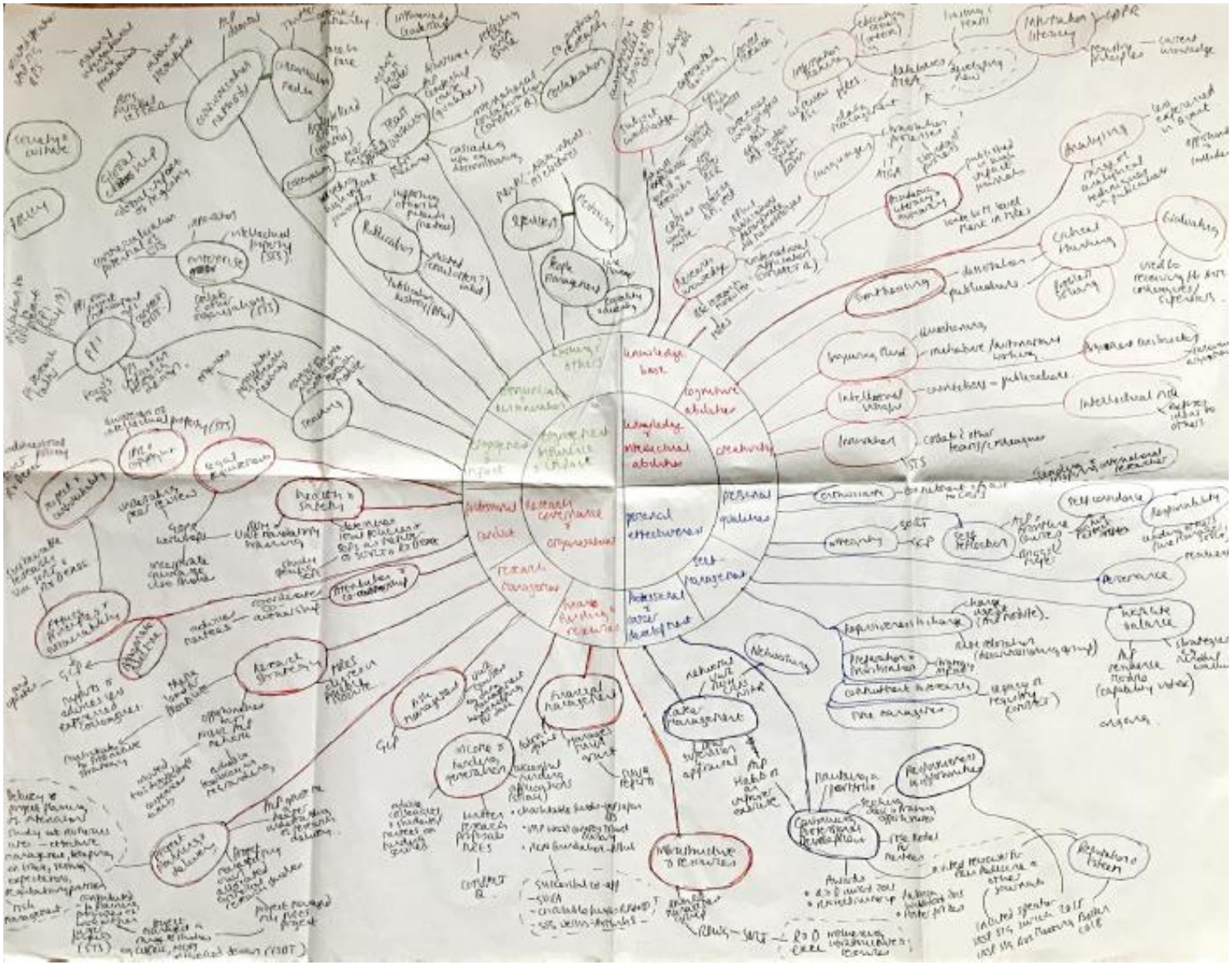
1.3.3. Application of the RDF to my professional development

The applicability of the RDF was explored to ensure that it could be used to effectively demonstrate my professional research development. The following stages were employed to tailor the RDF to the specific needs of my thesis, and these are summarised in Table 1.4, p11.

1.3.3.1. Stage 1: Mapping using a spider diagram

The first stage comprised the use of a spider diagram to map and represent my professional development throughout my career (Figure 1.2). Spider diagrams are commonly used as a knowledge representation system and enable the user to assimilate a range of data into meaningful information for decision making (Dua and Fish, 2008; Lancaster and King, 1999). In this way, I was able to construct a powerful visual schema of my research journey and one which demonstrated the range of skills, experiences and opportunities I have attained. It also provided an indication of where I should focus future development. Colour was used to distinguish my development within the four RDF key domains.

Figure 1.2: Spider diagram



1.3.3.2. Stage 2: Confirmation of RDF sub-domain attainment

This stage identified when a RDF sub-domain was achieved, in relation to each publication presented in the thesis. An overarching table was formatted with rows which listed all twelve sub-domains and their associated descriptors, and with columns which represented each of my eight publications. As each descriptor was achieved, the corresponding item was marked. The completed table provided confirmation that all twelve sub-domains had been considered (Appendix 4). This novel approach was an effective way to use visual representation to evaluate my professional and personal development.

1.3.3.3. Stage 3: Identification of sub-domain descriptors achieved for each publication

The final stage tabulated the sub-domain descriptors that were achieved for *each* publication. A table is presented as the final section of the critical commentary accompanying each publication.

These three stages demonstrate the innovative way in which the RDF can be applied to support a doctoral thesis retrospectively, as opposed to mapping professional development prospectively, at the outset of doctoral studies.

Table 1.4: Application of the RDF to my professional research development

Stage	Action
1	Using a spider diagram, with the four key domains and twelve sub-domains at the centre (Figure 1.2), I mapped my development throughout my research career.
2	An overarching table, which comprised all twelve sub-domains and their associated descriptors, provided confirmation that all twelve sub-domains had been considered for each of my eight publications (Appendix 4).
3	The descriptors achieved for each sub-domain are tabulated within the critical commentary for each publication. As the commentaries progress, newly achieved descriptors are highlighted in **bold.**

1.4. My career as a researcher

My professional role has enabled me to gain substantial experiential learning around the practical conduct of clinical research and the theoretical knowledge that underpins research practice. This section will describe my early development as a nurse researcher, my current research setting and present role, and will use the RDF to evidence my personal and professional development.

1.4.1. My early development as a nurse researcher

Evidence-based care has always been at the heart of my clinical practice and early in my career I recognised the importance of the dissemination of research findings to optimise outcomes for patients (Curtis *et al*. 2017). As a newly qualified nurse, I published a narrative paper promoting best practice in an oncology setting (Hanham 1990). From 1999 - 2003, whilst working clinically on a specialist Rheumatology ward, I studied part-time for a BSc (Hons) Professional Studies at the University of the West of England (UWE). This was my first introduction to research methodology and initiated my interest in research nursing. My first experience of the clinical research environment was my appointment, in 2003, as a Clinical Research Nurse (CRN) delivering predominantly commercial research studies within a Rheumatology Clinical Trials Unit. This taught me many skills including the importance of accurate and timely reporting of data, specialist clinical measurement, and managing my own caseload of clinical trials. Training in Good Clinical Practice (European Medicines Agency, 2016) has provided me with a robust knowledge of the ethical, scientific and practical standards to which all clinical research should be conducted to ensure research participants' rights, safety, and well-being are protected and research data are reliable (NIHR, 2019b). My role as a CRN plays to my strengths of being very organised, paying attention to detail and naturally adopting an analytical approach to my responsibilities and caseload. These attributes encouraged me to seek an extended CRN role where I could contribute to the design and reporting of research, and actively enhance my professional development (RDF B3).

In 2010, my appointment as the CRN for the national NHS England CRPS service in Bath, UK, was the springboard for my clinical academic career. Originally situated within the Royal National Hospital for Rheumatic Diseases in central Bath, it is now located at the Royal United Hospitals Bath NHS Foundation Trust (RUH). This interdisciplinary CRPS service is one of the few in the UK dedicated to the

treatment of CRPS, providing outpatient and inpatient care. Patients are referred from services across the UK and overseas. Research is firmly embedded within the service and there is an extensive portfolio of studies including international collaborations (publication 3, 6 & 7). In this appointment, I began to develop a more significant role, delivering academic, non-commercial research, and further developing specialist subject knowledge in the field of chronic pain and CRPS (RDF A1 - see Figure 1.1, p.8). This included data analysis and dissemination of findings.

One of my key objectives in the role of CRN in the CPRS service was to gain a deeper understanding of research methodologies, in terms of theoretical knowledge and practical application (RDF A1). After scoping the opportunities available to me, I applied to undertake a part-time Masters in Clinical Research. A particular advantage of this was that I would not only develop the necessary skills to successfully deliver health related research, but I would also achieve another of my key objectives which was to attain more of a leadership role (RDF D1), while still maintaining the connection with the clinical setting. In 2011, I was awarded a competitive National Institute for Health Research (NIHR) studentship to undertake a MRes Clinical Research at the University of Southampton, completing this in 2013. On completion of this Masters I had: acquired an in-depth understanding of the theoretical aspects of supporting and managing clinical research (RDF C2), increased my understanding of the national research strategy (RDF C2), and increased my contribution to the CRPS research portfolio. My involvement included more effectively contributing to the design of studies in the CRPS portfolio, testing existing theories (publication 3, p.42), and then analysing the data (publication 3, p.42) (RDF A3). Studying for my MRes also facilitated the development of my presentation and academic writing skills, and gave me the confidence to co-author a narrative paper. The paper aimed to raise awareness of CRPS and to provide nurses with information on how to diagnose and manage the condition (Grieve and McCabe, 2012).

In 2014, an honorary contract with UWE as a Visiting Research Fellow opened the way to a new network of academic colleagues from a range of disciplines. This met one of my key objectives, which was to build on opportunities to collaborate with UWE colleagues. The honorary contract was vital in gaining access to resources and training. It continues to the present.

At this time I also identified that, although I was taking on more responsibility, I still needed to build on the leadership skills which I had developed throughout the MRes. I was co-lead of an international study and I recognised that I had the potential to increase my effectiveness both in delivering research and also when line-managing junior colleagues. In order to address this, in 2014, I was successful in my application to attend the Frontline Leadership Course for Nurses and Midwives led by the NHS Leadership Academy. This was a useful introduction to leadership strategies. However, I was the only research nurse in the large cohort and therefore had limited shared experience with colleagues who were working in very different clinical settings.

In 2015, I identified an international training opportunity at the European Pain Federation Montescano Pain School in Italy. This would enable me to address one of my professional objectives, which was to develop my specialist diagnostic and neurological assessment skills including quantitative sensory testing (QST) (Rolke *et al*. 2006). QST uses a standardised range of diagnostic and assessment tools to characterise the somatosensory signs and symptoms of each patient. QST facilitates understanding of the underlying mechanisms of neuropathic pain and other chronic pain conditions, guiding diagnosis and treatment (Rolke *et al*. 2006). As the study of neuropathic pain is highly relevant in relation to my patient group, I recognised the importance of standardising diagnostic and assessment tools to facilitate the synthesis of data and develop best practice. I was awarded a competitive place at the prestigious Montescano Pain School. This week-long training, alongside health professionals from a range of European countries, provided the opportunity for shared learning and to establish networks for future working. The practical opportunities to undertake training in QST at the Pain School have enabled me to apply the underpinning knowledge to my clinical and research practice in a chronic pain population.

Still mindful of the need to extend my research-specific leadership skills, I more recently identified a new programme aimed at developing national leaders within the clinical research delivery workforce. In 2017 I was awarded a competitive place on the NIHR Advanced Leadership Programme (ALP) (NIHR, 2020a) which was a platform to accelerate my development as a research leader. This comprised three residential modules and weekly group learning activities throughout the 11-month programme. Participation has significantly extended my research networks nationally, provided me with a deeper understanding of the

research delivery system, and has given me the confidence to collaborate across organisational boundaries. The ALP supported me to improve self-management techniques, for example, building personal qualities such as increased resilience to work-life pressures, and making time for self-reflection in order to improve my performance as a researcher (RDF B1;B2)

1.4.2. My research setting

The national NHS England CRPS service is the focus for much of my research. The service has an internationally recognised, interdisciplinary clinical research team with a large portfolio of studies supported by NIHR, charitable and international funding bodies. Collaborations are well-established with academics at UWE, and other national and international organisations including the CRPS International Research Consortium (IRC) and the International Association for the Study of Pain (IASP) Special Interest Group for CRPS. In addition, collaborations exist with research groups and charities creating assistive technologies; for example, a long-standing collaboration with Designability (https://designability.org.uk/) has facilitated the ongoing development of a sensory training device for people with CRPS to use in the home (Grieve *et al*. 2015a). These long-established networks have enabled me to build connections and collaborate with internationally recognised researchers in the field of chronic pain and CRPS. Being affiliated with a widely-published and internationally recognised research team has enabled me to capitalise on these connections and co-lead an international research study.

1.4.3. My current role

I am the Pain Lead Research Nurse at the Royal United Hospitals Bath NHS Foundation Trust and a NIHR 70@70 Senior Nurse Research Leader (NIHR, 2019c). The Trust and NIHR roles are divided across my working week however, they inform and complement each other. My Trust role includes the identification of new research opportunities, funding applications, project management, delivery of funded research, support of clinical research trainees and contribution to the Trust's research strategy. This role includes the line management of junior research staff who support the delivery of the research programmes. I am a member of my NHS Trust's senior research team for operational issues and the R&D Executive Committee, where I am able to play a key role in shaping research practices throughout the Trust. My NIHR 70@70 role is described in more detail in

section1.4.3.2. The three key elements of my roles; research, leadership and education, are introduced below.

1.4.3.1. Research

As the measurement theme lead of PROactive (Pain, Rehabilitation and Innovation): a collaborative, interdisciplinary, NHS and university research network; I am in a key position to develop collaborative research opportunities in a variety of settings (https://www1.uwe.ac.uk/hls/research/healthandclinicalresearch/researchthemes/proactive.aspx). My role includes promoting the research to ensure wider impact of research findings and working with other network members to identify future research priorities (RDF D3). My own research situated within this theme includes the development of the first core outcome measurement set for CRPS which captures the psychological and physical nature of the condition (publication 6, p.59)

I am co-lead for an international study that is developing the first international CRPS clinical research registry. I am also currently co-leading a multicentre, international feasibility study to test the practicalities of collecting patient-reported questionnaire outcome data that will inform the final registry domains (publication 7, p.69). This requires high level project management skills and the ability to communicate effectively with colleagues from different cultures and health systems.

I am a co-applicant on a funded Versus Arthritis Medical Technologies Proof of Concept grant, and I co-lead the clinical study within this programme of work. This builds on previous work which developed a prototype sensory training system for CRPS (Grieve *et al.* 2015a). This programme aims to develop a novel product for commercial benefit and I have contributed to the negotiations with commercial companies to move this forward (RDF D3).

1.4.3.2. Leadership

In September 2019, I commenced my role as a NIHR 70@70 Senior Nurse Research Leader, as part of the NIHR 70@70 Senior Nurse and Midwife Research Leadership Programme (NIHR, 2019c). I applied for this competitive programme because, although my previous leadership training had enabled me to take on more responsibility and have a greater impact within the Trust, I wished to extend

my influence as a nurse research leader within the national research community. As an alumnus of the NIHR ALP, I was in a key position to apply for this role as I had increased my personal effectiveness as a leader; become more resilient, better able to communicate my vision, and able to secure the enthusiasm and commitment of team members. I was ready for a greater challenge and wished to build on my existing skills in relation to research leadership and service development.

My 70@70 role enables me to play a key role in raising the profile of research nurses and midwives, both within my own organisation and the wider NHS Nursing and Midwifery communities. With two working days per week dedicated to this programme, this is a leadership and career development opportunity and is a significant extension of my responsibilities. The role broadens my influence on research strategy beyond the Trust into the wider healthcare setting in the South West region. The role includes supporting nurses and midwives to engage in research, encouraging research collaborations and developing improved clinical academic career pathways. Working with senior research leaders nationally, I am able to contribute to shaping the NIHR priorities so that resources are focused on areas of clinical need.

1.4.3.3. Education

The CRPS service hosts placements for UWE undergraduate nursing and allied health professional research elective students and Versus Arthritis interns. I am a mentor on these programmes, co-designing project work, supervising students undertaking research projects, and supporting them in preparing abstracts for national conferences and in co-authoring academic articles (see publication 8, p.78). I have been a visiting lecturer on the Nursing Associate Apprenticeship research module at UWE, presenting the role of the research nurse and an introduction to qualitative research.

1.5 Summary of Chapter 1

The chapter has presented the overall aims of this thesis. I have introduced the RDF (Vitae, 2010) and described how I have applied this to my thesis to demonstrate my personal and professional development as a researcher. I have presented my early development as a nurse researcher and introduced my current research setting and professional role.

CHAPTER 2: Chronic Pain and Complex Regional Pain Syndrome

2.0 Overview of Chapter 2

The previous chapter presented the overall aims of this thesis. I described how I will apply the RDF (Vitae, 2010) to my thesis to demonstrate my personal and professional development as a researcher. I presented my early development as a nurse researcher, and introduced my current research setting and professional role.

Chapter 2 will critically appraise current literature in the field of chronic pain and Complex Regional Pain Syndrome (CRPS) where relevant to this thesis. Gaps in knowledge will be identified. CRPS exhibits similar clinical manifestations as other rheumatology conditions and this will be described, in order to contextualise the potential broader relevance of my research.

2.1 The nature of chronic pain

2.1.1 What is pain?

The current International Association for the Study of Pain (IASP) definition of pain is:

'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (IASP, 1979).

However, recent debate within the pain community (Apkarian, 2019; Treede, 2018; Tesarz and Eich, 2017; Williams and Craig, 2016) has identified the need to revise the current definition of pain. This is due to advances in the understanding of the mechanisms and management of pain; from both a multidisciplinary and biopsychosocial perspective (Williams and Craig, 2016).

A new definition was more recently proposed by an IASP Council Task Force;

'An aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury' (IASP, 2019)

Comment has been invited from the pain community. The new definition addresses current thinking for example, the description 'unpleasant' has been reframed as 'aversive', giving more significance to the experience of severe pain. Pain and nociception have also been recognised as different phenomena,

acknowledging that pain cannot be reduced to activity in sensory pathways (IASP, 2019). In addition, notes accompanying the proposed definition acknowledge the social aspect of pain and its potential impact on pain behaviours (IASP, 2019).

The outcome of the consultation has yet to be published therefore within this thesis the 1979 definition will apply.

2.1.2 The difference between acute and chronic pain

The purpose of acute pain is to protect the body from actual or potential harm and it is often the first sign of damage or the risk of damage. It induces the sufferer to take action by moving away and protecting the area of the body under threat.

For many people, acute pain resolves once the body has healed. However, for some, maladaptive changes occur in the nociceptive pathways of the central and peripheral nervous systems transitioning the change from acute to chronic pain (Fregosa *et al*. 2019; Chapman and Vierck, 2017), see Chapter 2; 2.2.1

2.1.3 Defining chronic pain

Throughout this thesis the term 'chronic pain' will be used as it is the terminology used by both the National Institute for Health and Care Excellence (NICE) and IASP; the latter being an internationally recognised organisation leading the study of pain (Treede *et al.* 2015; NICE, 2018). However, it is acknowledged that the terms chronic / persistent / long-term pain are used by health professionals interchangeably (BPS, 2015).

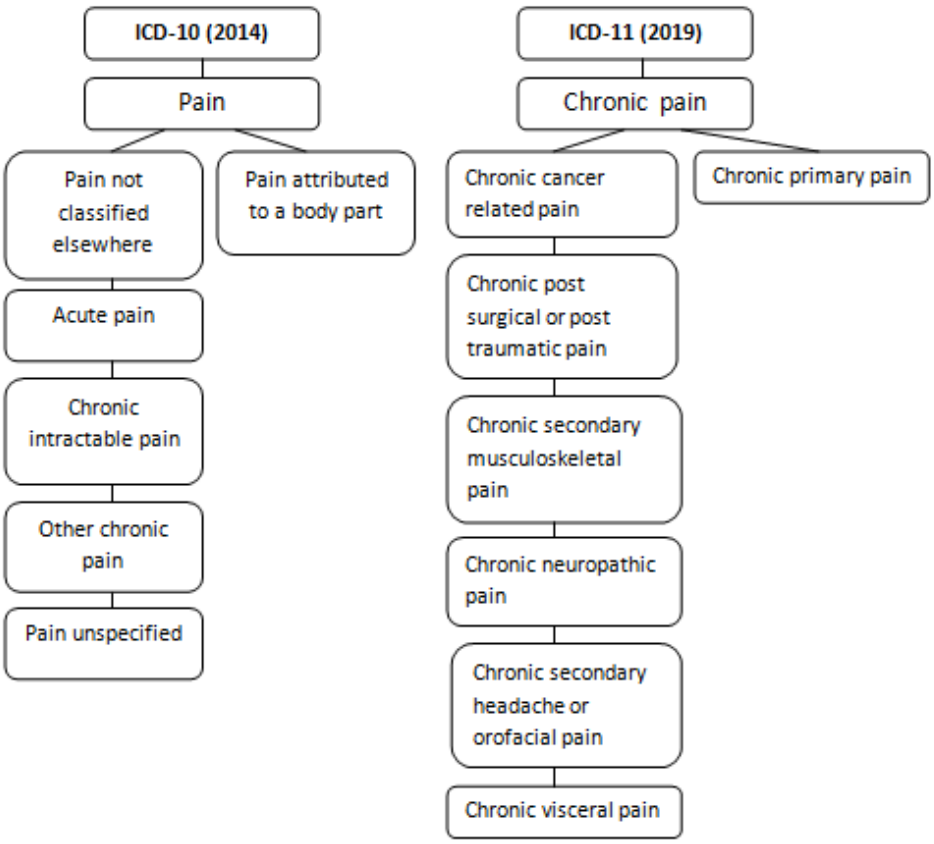
A collaboration between the World Health Organisation (WHO) and IASP have recently agreed a new classification for chronic pain as part of the 11th revision of the International Classification of Diseases (ICD)[1] (WHO, 2020). This thesis will use the WHO ICD-11 definition of chronic pain, which is: 'pain that persists or recurs for longer than 3 months' (WHO, 2019).

[1] The International Classification of Diseases (ICD) is the international standard for reporting diseases and health conditions, and provides the diagnostic classification for clinical and research use (WHO, 2020). This is important as it enables standardised data to be shared internationally. It is used by health professionals, health managers, patient organisations and policy makers (WHO, 2020).

The previous version, namely the ICD-10, coded chronic pain according to the body part affected rather than as an independent condition (WHO, 2014) (Fig. 2.1). In the ICD-11, chronic pain is now the 'parent' diagnostic code under which the seven chronic pain conditions, considered most clinically relevant, are coded (Treede *et al*. 2019) (Fig. 2.1). Highly relevant to this thesis is where pain is the leading or only symptom and this is classified as chronic primary pain (Nicholas *et al.* 2019). Examples of chronic primary pain include: (1) fibromyalgia (FMS), a condition manifesting in widespread musculoskeletal pain (Wolfe *et al*. 2010) and (2) CRPS, a chronic pain condition usually affecting a single limb (see section 2.4).

This new classification recognises chronic pain both as a health condition in its own right and also as a symptom of underlying disease (Sukel, 2019). This may have a positive impact on patient care because attribution of the correct diagnostic code may facilitate referral processes and enable patients with chronic pain to access the most appropriate treatment pathway. The new classification will also make it easier to measure prevalence of chronic pain, which may inform healthcare policy.

Fig.2.1: Comparison of the ICD-10 and ICD-11 (WHO 2014;2020)



2.1.4 Aetiology and epidemiology of chronic pain

Prevalence of chronic pain is difficult to ascertain. Reasons for this include epidemiological studies which often comprise (1) study populations with a range of complex chronic pain experiences, including high functioning individuals and those who are significantly debilitated (Fayaz *et al.* 2016; Kennedy *et al.* 2014; Reid *et al.* 2011) and (2) study populations using different criteria to define chronic pain (Steingrímsdóttir *et al.* 2017). Illustrating this challenge, a recent meta-analysis of epidemiological studies found prevalence estimates ranged from 8.7% to 64.4%; however, a pooled mean of 31% was reported, albeit from a predominantly European population (Steingrímsdóttir *et al.* 2017). An earlier survey conducted in the United States found a lower prevalence, with approximately 19% of adults reporting frequent or constant chronic pain (Kennedy *et al*. 2014). In the UK, Fayaz *et al*. (2016) conservatively suggested chronic pain affects between one-third and one-half of the population. This was a high quality study conducted according to the PRISMA guidelines for the reporting of SLR's (Liberati *et al*. 2009).

The economic burden of chronic pain is high, with health service expenditure three times higher for this population than those without chronic pain (Moore *et a,* 2014; Ivanova *et al.*2011). In the US this equates to nearly $635 billion annually (Murphy *et al*. 2017). Further economic impacts stem from pain-related absenteeism, poor productivity and inability to work (NICE 2018; Goldberg and McGee, 2011).

2.2 The mechanisms of chronic pain

The mechanisms which drive and maintain chronic pain are complex. This section will briefly describe current understandings where relevant to the research presented in this thesis, specifically publication 3 (p.42).

2.2.1 Peripheral and central sensitisation

Key mechanisms underlying chronic pain are peripheral and central sensitisation (CS) (den Boer *et al.* 2019; Arendt-Nielsen *et al*. 2018). Sensitisation results when a normally innocuous stimulus is perceived as painful due to an increased response by the sensory nervous system (Borstad and Woeste, 2015). This neural process of encoding noxious stimuli is described as nociception (Loeser and Treede, 2008). A persistent nociceptive stimulation in the peripheral nervous system, can lead to peripheral sensitisation (Borstad and Woeste, 2015). If the

stimulation is prolonged, central sensitisation occurs (Nijs, Van Houdenhove and Oostendorp*,* 2010).

CS is described as an impaired functioning of anti-nociceptive mechanisms and over-activation of ascending and descending pain pathways in the central nervous system (Nijs *et al*. 2011). Clinically, this manifests as pain extending beyond the period of noxious stimulation (Goebel, 2011). CS may contribute to the transition from acute to chronic pain, as well as maintaining chronic pain (Fregosa *et al*. 2019; Arendt-Nielsen *et al*. 2018).

2.2.2 Sensorimotor incongruence

The sensorimotor cortex of the brain is constantly processing and integrating the sensory information received from our body, in order to inform and produce a motor response (Foell *et al.* 2013; Flanders, 2011; McCabe *et al*. 2009). This sensory and motor information is directly linked to the autonomic nervous system and, when sensory input is perceived as a threat or stress, a motor response is produced in order to keep us safe, for example, withdrawing a hand away from a hot surface. (Knudsen *et al.* 2019; Moseley *et al.* 2008).

Continually learning from experiences (Wei and Kording, 2009), the sensorimotor system uses prediction to anticipate and adapt to changes so that our functioning is maintained at an equilibrium. Inconsistency between sensory input and motor integration is called a sensorimotor incongruence, and it can result in pain and other sensory disturbances; not only for those with chronic pain (Knudsen *et al.* 2019; Don *et al.* 2016; McCabe *et al*. 2009) but also healthy individuals (Brun *et al*. 2018a; McCabe *et al*. 2005).

The main sensory disturbance described in the literature is a sense of incomplete body representation such as perceiving swelling where none is evident clinically and perceived changes in the weight of a limb (Moseley, 2008; McCabe *et al.* 2007; McCabe *et al*. 2000). These changes have been reported in different patient populations including chronic low back pain (Moseley, 2008), CRPS (Brun *et al.* 2018b; Peltz *et al.* 2011; Lewis *et al*. 2007), FMS and RA (Brun *et al.* 2018b; Valenzuela-Moguillansky, 2013; McCabe *et al.* 2000). Sensory disturbances have been found to be more frequent and intense in people experiencing chronic pain than those without (Don *et al*. 2017).

Despite numerous studies, the mechanisms underpinning the relationship between sensorimotor incongruence and pain are unclear and need to be explored further (Don *et al.* 2017). Several theories have offered accounts for these sensory disturbances. A seminal paper by Harris (1999), supported by Don *et al 2016,* hypothesised that the presence of sensorimotor incongruence may contribute to pain and other sensory disturbances in chronic pain pathologies for example, phantom limb pain. Later studies have demonstrated how, in the presence of pain, sensorimotor conflicts induce a temporary increase in pain, and other sensory disturbances (de Kooning *et al.* 2016; Brun *et al.,* 2017). This suggests sensorimotor conflicts could contribute to the maintenance of pain (McCabe *et al*. 2007). This will be discussed further in Publication 3 (p.42).

2.3 Chronic pain in the context of rheumatology

Chronic pain is a frequently reported symptom in rheumatology. It arises from mechanisms which include persistent inflammation, structural changes to the musculoskeletal system or diseases of the motor nervous system (Treede *et al.* 2019)

Examples of chronic pain conditions within rheumatology include; Rheumatoid Arthritis (RA), FMS and CRPS (see section 2.7). These conditions exhibit similar clinical manifestations, such as a fatigue and/or muscle weakness (Bucourt *et al.* 2019; Yamada *et al.* 2017; Watson *et al.* 2009; McCabe *et al*. 2004). All have chronic pain as the principal feature and predominantly affect women, with a comparable peak onset age (Birklein, O'Neill and Schlereth, 2015).

Despite clinical similarities, the recently published ICD-11 differentiates between rheumatology conditions (WHO, 2020). FMS and CRPS are classified as primary chronic pain conditions, as the pain cannot be better accounted for by another identifiable causative pathology (Nicholas *et al.* 2019). RA is classified as a chronic secondary musculoskeletal pain because it arises from a disease process directly affecting the musculoskeletal system (Perrot *et al*. 2019).

2.4 Complex Regional Pain Syndrome

2.4.1 Background

CRPS is a chronic pain condition, affecting a limb. Its name provides an indication of the multifaceted nature of the disorder. Intense, burning pain is the predominant symptom however, other features include changes to limb temperature, colour, nail and hair growth, and impaired limb function. In approximately 7% of cases, CRPS can spread to other limbs (Goebel *et al*. 2019; van Rijn *et al*. 2011). There is no cure but early intervention should significantly improve outcomes (Gillespie *et al.* 2016; Birklein *et al*. 2015).

There are two types of CRPS, distinguishable by the absence (Type 1, more common) or presence (Type 2) of major nerve damage (de Mos *et al*. 2007).

The aetiology of CRPS is unknown; however, precipitating factors include trauma and surgery (Harden *et al.* 2010). It is likely the aetiology has many components including inflammation, dysfunction within sympathetic and somatosensory nervous systems, and changes within the cortex of the brain (Birklein *et al*. 2015). Despite recent challenges in the literature (Chang, McDonnell and Gershwin, 2019), there is no evidence of a psychological origin or of anxiety and depression as predictors (Beerthuizen *et al*. 2012; Beerthuizen *et al*. 2009). However, psychological symptoms, such as anxiety and depression, frequently develop if the condition persists (Goebel, Barker, Turner-Stokes *et al*. 2018; Bean *et al*. 2016a).

As there is no definitive test for CRPS, diagnosis is based on the Budapest diagnostic criteria (Harden *et al.* 2010) (Table 2.1, p.25). Recent European standards for the diagnosis and management of CRPS strongly recommend use of these criteria as they provide sufficient sensitivity and specificity to confirm the diagnosis (Goebel *et al*. 2019).

Table 2.1: Budapest diagnostic criteria for CRPS (Harden *et al*. 2010)

<table>
<tr><td colspan="2">All of the following MUST apply:
The patient has continuing pain which is disproportionate to any inciting event
The patient has at least one sign in two or more of the categories
The patient reports at least one symptom in three or more of the categories
No other diagnosis can better explain the signs and symptoms</td></tr>
<tr><td colspan="2">Categories</td></tr>
<tr><td>Sensory

Allodynia[a] (to light touch and/or temperature sensation and/or deep somatic pressure and/or hyperalgesia (to pin prick)</td><td>Sudomotor/ oedema

Oedema and/or sweating changes and/or sweating asymmetry</td></tr>
<tr><td>Vasomotor

Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry</td><td>Motor/ trophic

Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/skin/nails)</td></tr>
</table>

[a] Allodynia is defined as pain in response to a stimulus which is not normally painful.

Recent literature has challenged the legitimacy of CRPS as a condition, for reasons including over-diagnosis, due to the lack of specificity of the diagnostic criteria, and the absence of an objective test for CRPS (Chang, McDonnell and Gershwin, 2019; Borchers & Gershwin, 2017). Although, several papers presenting this view have been published in the past few years, there is reason for caution as they present opinion from the same contributing author.

The European incidence of CRPS is 20-26/100,000 person years (de Mos *et al.* 2007) which equates to approximately 17,000 people in the UK each year

developing CRPS. However, these data are over 10 years old and require updating.

Although many cases will resolve within 6 to 13 months, a recent systematic review found that between 22% and 64% of patients experience persistent symptoms ≥3 years after diagnosis (Bean, Johnson and Kydd, 2014b). Living with CRPS has a significant impact on health related quality of life (van Velzen *et al*. 2014) and can lead to significant long-term disability and mental health issues which disrupt employment and family roles (Bean *et al*. 2016b; 2014a).

A recent retrospective analysis of the Swiss National Accident Insurance database reported high economic costs associated with cases where CRPS was diagnosed. (Scholz-Odermatt *et al*. 2019). Comparisons found (1) average treatment costs after accidents were 13 times higher for people with CPRS and, (2) the number of working days lost within the first two years after the accident, was 20 times higher in people with CRPS than those without CRPS. It is unclear if this would translate to a UK population as published comparative data is unavailable.

2.4.2 Body perception disturbances in CRPS

In common with other chronic pain conditions, sensory disturbances are commonly reported by those with CRPS (Lewis *et al*. 2007). For example a person may describe a 'burning hot' sensation in their limb, when it is actually cool to the touch; or report a sensation that parts of the limb are missing; or a sense that the limb is bigger than it is in reality (Peltz *et al*. 2011; Lewis *et al*. 2007; Moseley, 2005). These sensory disturbances are termed Body Perception Disturbances (BPD), and can be confusing for the individual and difficult for the patient to describe to a health professional (Lewis *et al*. 2007). In addition, patients may feel hesitant in sharing these experiences for fear of not being believed (Lewis *et al*. 2007). This is explored further in Publication 2 (p.36).

The cause of BPD is unclear and there are conflicting views. Early imaging studies demonstrated remapping of the CRPS affected limb in the primary somatosensory cortex (Vartiainen *et al.* 2009; Pleger *et al*. 2004; Maihőfner *et al*. 2003). A more recent review of the evidence in CRPS by Swart, Stins and Beek (2009) supported the premise that BPD result from cortical reorganisation. This hypothesis has informed treatments aiming to reverse the changes to the cortical

map to pre-CRPS status, for example mirror therapy (McCabe *et al.* 2003) and desensitisation (Moseley, Zalucki, and Wiech, 2008).

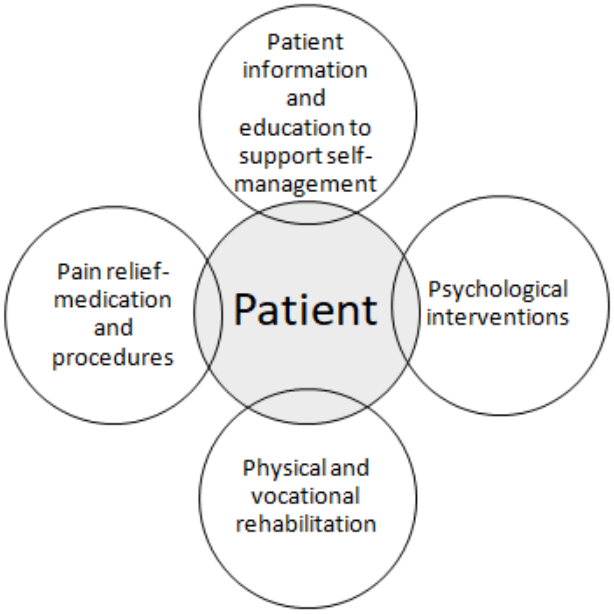
However, recently this hypothesis has been challenged (Mancini *et al*. 2019; Di Pietro *et al*. 2013). A literature review found that much of the evidence reporting cortical reorganisation in CRPS originated from a few studies only and that, due to indistinct sampling methods and unblinded analysis, there was a risk of bias (Di Pietro *et al*. 2013). A further recent study reported the spatial map of the fingers, in the primary somatosensory cortex in chronic CRPS, is comparable to that of a pain-free control group (Mancini *et al*. 2019). Using lower resolution imaging techniques than available in previous work (Vartiainen *et al*. 2009; Pleger *et al*. 2004), this provided a more accurate measure of the hand map, finding it to be not related to pain or disease severity (Mancini *et al.* 2019). Whilst the findings of Mancini *et al*. (2019) and Di Pietro *et al*. (2013) challenge the treatment rationale for restoring cortical representation of the limb in CRPS patients, future research should establish if these results can be replicated.

2.4.3 Management of CRPS

UK recommendations for the diagnosis, referral and management of CRPS in adults, in primary and secondary care have recently been updated (Goebel, Barker, Turner-Stokes *et al*. 2018). An integrated, interdisciplinary, treatment approach is recommended with the primary aim to reduce pain, restore or preserve limb function, and promote self-management (Goebel, Barker, Turner-Stokes *et al*. 2018). Although these recommendations of best practice are published, little is known about the reality of provision of care, regionally and nationally, and if the guidelines are being adopted in clinical practice. This will be discussed further in Publication 8 (thesis p.78).

The UK guidelines (Goebel, Barker, Turner-Stokes *et al.* 2018) describe and recommend four approaches or ‘pillars of care’ (Fig. 2.2). A core component is the provision, to patients, of information to educate them about CRPS and its management (see publication 4, p.48). However, there is evidence of conflicting and outdated information provided by some health professionals (Louw *et al*. 2018; Rodham *et al*. 2016; Rodham *et al.* 2013).

Fig. 2.2: Four pillars of care for CRPS



From a wider European perspective, the CRPS European Pain Chapters Task Force has recently published the European standards for the diagnosis and management of CRPS (Goebel *et al.* 2019). These are an important step forward because, as well as providing a benchmark for best practice, they can be used by stakeholders to target resources appropriately. It will be several years before the impact of these standards is known.

2.4.4 Limitations of current methodological approaches in CRPS research

In 2013, CRPS was categorised as an "orphan disease" on the basis that fewer than 200,000 people in the United States, and fewer than 154,000 people in the European Union, are affected with CRPS each year (US Food and Drug Administration, 2013; European Medicines Agency, 2013). Patient recruitment for CRPS clinical studies therefore presents significant challenges, due to low prevalence and a heterogeneous patient population. A criticism directed at CRPS research is that studies are conducted and reported with insufficient sample sizes to achieve statistical power (Chang, McDonnell and Gershwin, 2019; Borchers and Gershwin, 2017). This reinforces the need for multi-centre collaborative research to attain sufficient sample sizes for meaningful studies.

A further limitation is that CRPS clinical trials do not currently collect a standardised set of outcome measures. Instead, a wide range of patient-reported questionnaire outcome measures are used which has precluded the synthesis of clinical research evidence and impeded the understanding of the mechanisms of

CRPS and potential therapeutic interventions (Wertli *et al*. 2014; O'Connell *et al*. 2013). This will be discussed further in publication 5 (p.54).

The issues in CRPS are reflected in a paper by Chiarotto *et al.* (2017) reporting how the use of inconsistent measures not only hampers the ability to pool results and conduct meta-analyses but also risks selective reporting bias of favourable outcomes. In addition, the outcome measures used have not always included those that matter the most to patients themselves (Porter, Larsson and Lee*,* 2016; Turk *et al*. 2008).

2.4.5 Initiatives for the development of core outcome measurement sets (COMS)

To promote comparability and quality of research data, it has been recommended that standardised, validated, core outcome measurement sets (COMS) should be reported in all clinical studies (Boers *et al*. 2014; Williamson *et al*. 2012). It is recommended COMS are agreed by consensus by relevant stakeholders, which includes the relevant patient group (Tugwell *et al*. 2007).

Two initiatives have led the way in chronic pain and rheumatology for the development of COMS: 'Outcome for Measures in Rheumatology' (OMERACT) (Boers *et al*. 2014),and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Turk *et al*. 2003). Each uses a different methodological approach however, with a shared aim to enable meaningful comparison across studies.

The starting point for both the OMERACT and IMMPACT initiatives was to agree which specific concepts or core domains, as appropriate to the population under study, should be measured to answer a specified research question (Boers *et al*. 2014; Turk *et al.* 2003). The second stage was to identify patient-reported outcome measures which would measure each domain. This methodological approach informed the work presented in Publication 6 (p.59).

2.4.5.1 Clinical research registries

Recent recommendations towards addressing the research challenges when studying an orphan disease population have been published, and include the establishment of clinical research registries (Fonseca *et al*. 2019). A registry is a collection of information from people with a specific health condition (NIH, 2020). It

provides a means of collating a large, uniform set of prospective data which can be from across a wide geographical area (Psoter and Rosenfeld, 2013). Clinical research registries are used widely in healthcare to provide researchers with access to retrospective data for interrogation of a specific health condition (Dasenbrook and Sawicki, 2018; Psoter and Rosenfeld, 2013).

Establishing an international, clinical research registry for CRPS would enable researchers to access a large, consistent, international dataset. This could be used to gain a better understanding of the mechanisms driving CRPS and inform targeted treatment approaches. This will be discussed further in publication 7 (p.69).

2.5 Summary of Chapter 2

This chapter has critically appraised current understandings in the field of chronic pain and CRPS as relevant to this thesis. In order to contextualise the potential broader relevance of my research, CRPS has been described in the context of rheumatology. Gaps in knowledge have been identified and will be addressed in Chapter 3.

CHAPTER 3: My publications

3.0 Overview of Chapter 3

The previous chapter demonstrated that I have a critical understanding of the current state of knowledge in the field of chronic pain and Complex Regional Pain Syndrome (CRPS). To contextualise the potential broader relevance of my research, CRPS was described with reference to the specialism of rheumatology.

Chapter Three will present the eight publications which comprise this thesis, each accompanied by a critical commentary of my individual contribution to the original research. Where new knowledge has been generated, this will be highlighted in the commentary and I will also describe my personal and professional development in relation to the publication and in the context of the RDF (Vitae, 2010). The original publications can be found in Appendix 1.

3.1 Publication 1

Publication	Text book	My contribution
McCabe, C., Gauntlett-Gilbert, J., **Grieve, S.,** Lewis, J., Walsh, N. (2018) **Multi-disciplinary Approaches to Managing Long-term Pain in Arthritis.**	In: ***Rheumatology*** Hochberg *et al.* (2018) *7th Edition.* Elsevier: Philadelphia, pp.434-438.	**Book chapter:** • Wrote specific sections of this chapter in relation to outcome measures and patient education • Contributed to the chapter as a whole to ensure my contributions were situated appropriately within the entire text • Reviewed the proof and made corrections

3.1.0 Background

Publication 1 is a co- authored chapter within the textbook of 'Rheumatology' (7th edition, Elsevier). The lead author had received an invitation from the Editors of this textbook for a significant re-working and updating of the text of this chapter from a previous edition (6th). I was invited to contribute to this as a result of my expertise in patient- reported outcome measures (Publications 5 & 6) and patient education (Publication 4). I already had experience as a lead author on a number of peer-reviewed publications (Publication 4, 5 & 6) so I was ready for a new challenge. The other contributing authors were academic and clinical colleagues with specialist knowledge in this field. As my contribution drew from existing published literature, it does not contribute to new knowledge within the thesis. It is included as one of my presented publications as it establishes my competence as an academic researcher. The book chapter is the first publication presented in Chapter 3 as it sets chronic pain in the wider context.

Chronic pain is one of the most frequently reported clinical symptoms encountered by rheumatologists (Fitzcharles & Shir, 2011; Masala *et al*. 2017). A multidisciplinary management approach of pain is advocated, which is based on the biopsychosocial model of pain. This approach has been shown to be clinically

effective and cost-efficient (Dysvik *et al*. 2010; Turk, 2002) but it is not always offered in a rheumatology clinical setting (Kress *et al*. 2015). This textbook chapter introduces the reader to chronic pain in the context of rheumatology and describes current multidisciplinary approaches used to address the sensory, emotional, behavioural and cognitive factors which influence the pain experience (Appendix 1, publication 1, introduction, p434). The textbook chapter may promote adoption of the multidisciplinary management approach more widely in healthcare.

3.1.1 My contribution to the textbook chapter

My contribution to the chapter comprised updating the sections entitled 'measurement of pain' (Appendix 1, publication 1, p434) and 'patient education and e-health' (Appendix 1, publication 1, p436). It was important that the chapter contained a synthesis of the most recent literature in these fields in order to effectively update the previous edition, including research evidence, current guidelines and standards (Aveyard, 2019). A narrative approach was appropriate in this context as I was presenting an in-depth review of the current literature as secondary evidence within a textbook.

There was no requirement to report the literature search method and search strategy within the text, as would be usual for a research publication of a systematic literature review, nevertheless, I used a systematic approach to ensure that the cited evidence was representative of the current knowledge and research in this area (Aveyard & Sharp, 2017). Using the chapter headings and my subject knowledge to inform the search terms, I searched the evidence using electronic databases in medical science. Critical appraisal of the search results ensured that the evidence was assessed and interpreted by systematically and objectively considering its quality, validity and relevance (Horsley *et al*. 2011; Aveyard, 2019). I then revised and extended the existing chapter text, ensuring that it remained accessible to a reader who may not have in depth knowledge of this topic.

In response to the Editor's directive, the subject knowledge within the chapter was embedded within the arthritis, rather than the CRPS, literature. Due to the limitations of the publisher-enforced word count, the intellectual challenge was how to refine the evidence to present only pertinent and highly relevant information. I planned my contribution carefully to focus on contemporaneous issues and ensured references were drawn from the wider musculoskeletal

chronic pain literature. I was able to utilise my clinical experience to describe the subjectivity associated with assessing the scale and intensity of a patient's pain.

Patient education had been included in the previous edition of the chapter however, informed by my knowledge gained from undertaking Publication 4 (p.48) I chose to broaden this version to include e-health. I addressed the role of the internet as a key source of health information in order to make the chapter relevant in today's society. Acknowledging the lack of studies assessing the efficacy of these approaches (Keogh *et al*. 2010; McGeary *et al*. 2012), I wanted to highlight how patient education and self-management strategies are increasingly becoming an interactive learning process rather than a one-way delivery of knowledge (Zangi *et al*. 2015).

3.1.2 Opportunities presented from this research

This publication provided an opportunity to collaborate with senior colleagues from the Faculty of Health and Applied Sciences at the University of the West of England and a local specialist pain service. Collaboration on the book chapter contrasted to my prior experience of co-authoring a journal paper; in the book chapter the individual contributions were combined together, whereas in the prior journal article, the lead author had taken responsibility for preparing the first draft of the full manuscript. Following amalgamation of the chapter by the lead author, I reviewed and amended the text to ensure that my contribution was situated seamlessly within the entire copy. I appreciated the process of synthesising the contributions of different authors with distinct writing styles. I reviewed the proof prior to publication and made corrections. Contributing to the 7th edition made me aware of how textbooks quickly become outdated, although the publisher has embraced technological advances and digital demands by providing an e-version. This experience taught me the difference between writing a chapter section and writing a journal paper. The latter can stand alone and is directed at a specialised audience usually with previous knowledge and experience whereas the former needs to be of interest to a wider readership. As a result of this publication, I was approached to submit a chapter idea for Meanings of Pain, Volume 2 (Springer). My commitments at that time meant that I declined, however, I intend to pursue future opportunities.

3.1.3 RDF domains achieved

Four RDF sub-domains were achieved whilst contributing to the textbook chapter presented in Publication 1 (Table 3.1).

Table 3.1*:* RDF sub-domains achieved in Publication 1

RDF Sub-domain achieved	Descriptor
RDF A1: Knowledge base	Subject knowledge
	Information seeking
	Information literacy and management
	Academic literacy and numeracy
RDF B2: Self-management	Preparation and prioritisation
	Time management
RDF D1: Working with others:	Team working
	Collaboration
RDF D2: Communication and dissemination	Publication

3.2 Publication 2

Publication	Journal and Impact Factor	My contribution
Turton, A., Palmer, M., **Grieve, S.,** Moss, T., Lewis, J. and McCabe, C. (2013) **Evaluation of a prototype tool for communicating body perception disturbances in complex regional pain syndrome.**	**Frontiers in Human Neuroscience.** 7 (517), pp.1-8. IF:2.871	**Study:** • Delivered the study in an NHS setting • Co-designed the standardised questionnaire • Contributed to the ethical approvals process • Conducted the Informed consent process • Recruited the study participants • Collected data using the digital tool and administered the standardised questionnaire • Contributed to the qualitative data analysis **Paper:** • Reviewed the peer reviewed manuscript prior to submission

3.2.0 Background

Publication 2 was an observational and qualitative proof of concept study, which evaluated the acceptability of a first prototype tool to enable patients to communicate body perception disturbance in CRPS (Lewis and Schweinhardt, 2012; Peltz *et al*. 2011; Lewis *et al*. 2007; Moseley, 2005), see Chapter 2, 2.4.2. This was an appropriate design for the first development stage of a new technology that sought to establish its feasibility and practical potential (Kendig, 2016). Publication 2 was my first experience of contributing to a manuscript presenting empirical research and is, chronologically, my earliest publication presented in this thesis. At this time I was confident in the delivery of clinical research studies, including data collection, however, this was my first involvement in questionnaire design and data analysis.

At the time of this research, CRPS patients in the clinical setting would typically be asked to describe their limb to enable the health professional to assess the nature of their body perception disturbance (Lewis and McCabe, 2010; Lewis *et al.* 2007; Moseley, 2005). However, the quality of the final representation of patients' altered

perceptions was limited by their capacity to articulate their perception of their limb. Further limitations were a consequence of the health professional often undertaking the drawing in response to the patient's description, with the resultant depiction potentially being far removed from the patient's' actual experience. Building on the work of others, where photographic images were manipulated using software to represent altered body perception (Rode *et al. 2012;* Halligan, 1999), it was proposed that digital media may provide a more suitable and accurate method for capturing changes in body perception. Use of an avatar offered the potential to provide a multidimensional, 3D tool, which would enable patients to describe the nature of their altered body perception more readily and would be more easily applied within a clinical setting. An avatar can be defined as a digital representation or icon, through which the user experiences the virtual world and which, in this instance, was presented in human form (Bell, 2008).

3.2.1 Collaboration

My involvement began shortly after I had been appointed as the CRN for the CRPS service, when the study was under NHS ethical review. This study provided one of my earliest experiences of inter-university collaboration, working with research partners from the Centre for Appearance Research and Computer Science and Creative Technologies at UWE and thereby extending my research network outside of Health and Applied Sciences. As an early researcher, this study presented an exciting opportunity to be at the forefront of new technologies for potential patient benefit. Until this point, I had only used well-established medical technologies within my clinical practice.

3.2.2 Study delivery

My responsibility was to deliver the study within the NHS setting. Liaising closely with the academic study lead at UWE I undertook all of the patient recruitment and the receipt of written informed consent prior to any study procedures being conducted. At this time I was experienced in patient recruitment processes however, I had less experience of obtaining informed consent. To ensure that I had the necessary skills I attended an 'introduction to valid informed consent in clinical research' study day provided by the NIHR Clinical Research Network.

3.2.3 Data collection

I co-designed the structured questionnaire (Appendix 1, publication 2, materials and methods, para 4) which would ascertain the participant's experience of using the tool. We chose to use standardised questions, with no variation, which were presented to respondents in the same way to ensure protocol fidelity across participants (Bowling, 2014). This was my first experience of contributing to the design of a questionnaire and, following feedback from my co-researchers, I gained an understanding of the value of open questions to enable the respondents to respond in their own words, rather than closed, pre-determined options. My contribution to the questionnaire design was limited by my inexperience, and I identified this as an area for future development.

The study data collection methods comprised a digital media tool (Appendix 1, publication 2, materials and methods, para 1), audio recording and a structured questionnaire (Appendix 1, publication 2, materials and methods, para 4). The opportunity to use a novel digital tool to capture patient's body perception, highlighted to me the opportunities offered by methods employed in disciplines outside of healthcare. I needed to develop technological prowess in a short space of time to: (1) become proficient with the specifications of this prototype system, (2) introduce the principles of the body perception tool (BPT) to the patient and (3) act on their instructions to translate their description to an image. I was responsible for accurately capturing the images created by the patient and securely storing these data. Data were pseudonymised, whereby the identifiers which were easily attributed to the individuals were replaced with a study identification number (ICO, 2019). I maintained a rigorous process of data management to ensure the resulting data could be utilised effectively by the research team (Gerrish and Lacey, 2010). For example, as a prototype the BPT had limitations, and I was responsible for recording potential improvements, identified by the patient and myself, on an Excel spreadsheet to inform future work.

I developed an ability to convey complex information in a comprehensible and standardised manner which better enabled the patient to understand what was required of them in describing their body perception. I was then able to accurately depict the image to the patient's satisfaction, without biasing the image with my own interpretation of the patient's description (Pannucci and Wilkins, 2010). It was

plausible that there was potential for the patient to become distressed whilst they communicated the changes to the avatar due to their perception of the limb conflicting with reality (Lewis *et al.* 2007), therefore consideration and sensitivity were needed at all times during this data collection process.

Working closely with a computer scientist, I was able to translate the protocol into practice. I learnt new skills in relation to computer science and digital media tools for example, how to operate the software and manipulate the avatar.

Qualitative data were collected from the responses to the questionnaire and the audio recording (Appendix 1, publication 2, materials and methods, section 4&5; Results section 2&3) As the researcher responsible for data collection, I was well-placed to contribute to the qualitative analysis as I had been immersed in these data over many months. I contributed to the discussions around the interpretation of the data, improving reliability (Green and Thorogood, 2011). However, I recognised my contribution to the discussions was limited by my knowledge of research paradigms and this inspired me to learn more about qualitative methodology (Publication 4).

3.2.4 New knowledge

This novel tool had the potential to directly impact CRPS clinical care as it allowed individuals to depict the alteration in body perception more accurately using a visual representation (Table 3.2). It offered an opportunity to capture this information pre and post-treatment, providing information to clinicians regarding outcomes of rehabilitation and in response to other factors such as pain. Following the study, the tool was used for several months by the Bath in-patient CRPS programme. However, in practice it was found to be time-consuming to implement within the practical limitations of the programme timetable. Furthermore, it did not offer a full range of descriptors required by the patients, for example more sophisticated depictions of sensation. Potential future software modifications were identified, to include the ability to manipulate individual digits on the avatar, add animation to represent sensations, and to accurately quantify the extent of the area affected. Since publication 2, the tool has been used to successfully communicate changes in body perception in stroke (Stott *et al*. 2019) which demonstrates how it has transferability into other conditions. However, limitations were also reported during use with this population, such as, it was perceived as

time-consuming by the study participants and had a complicated functionality for independent patient use (Stott, 2019).

Table 3.2: New knowledge generated from Publication 2

New knowledge generated	• A novel method of communicating changes in body perception was developed
	• A novel method of representing changes in body perception using digital media was developed

3.2.5 The publication

I reviewed the manuscript prior to submission for publication, editing and refining the text for clarity. I had a peer reviewed abstract reporting the study findings accepted as a poster presentation at an international CRPS conference (Grieve *et al.* 2012). I was awarded Runner-Up in the Bath Institute for Rheumatic Diseases Davies-Maitland Scholarship Prize for post-graduate researchers in 2012, in recognition of the study's contribution to patient care. The study team was also awarded the RUH Research and Development Award in 2015.

Publication 2 was the catalyst for my determination to gain experience in the early stages of study design. I had joined the research team after the methodology was agreed and in the future I wanted to play a more active role in the decision-making process. I was concurrently undertaking the MRes Clinical Research throughout the conduct of this study. The MRes provided me with a greater understanding of research methodology and I was able to directly apply this new knowledge in the conduct of this study, for example, obtaining informed consent and qualitative interview techniques.

3.2.6 RDF domains achieved

Nine RDF sub-domains were achieved whilst undertaking the research presented in Publication 2 (Table 3.3, p.41).

Table 3.3: RDF Sub-domains achieved in Publication 2

RDF Sub-domain achieved	Descriptor
A1: Knowledge base	Subject knowledge
	Research methods – theoretical knowledge*
	Research methods – practical application
	Information seeking
	Information literacy and management
	Academic literacy and numeracy
A2: Cognitive abilities	**Analysing**
A3: Creativity	**Inquiring mind**
	Innovation
B1: Personal qualities	**Integrity**
	Self confidence
B2: Self-management	Preparation and prioritisation
	Time management
B3: Professional and career development	**Networking**
C1: Professional conduct	**Ethics, principles and sustainability**
	Health and safety
D1: Working with others:	Team working
	Collaboration
D2: Communication and dissemination	Publication

***** Descriptors in bold are newly acquired as a result of this publication

3.3 Publication 3

Publication	Journal and Impact Factor	My contribution
Brun, C., Mercier, C., **Grieve, S.,** Palmer, S., Bailey, J. and McCabe, CS. (2018) **Sensory disturbances induced by sensorimotor conflicts are higher in complex regional pain syndrome and fibromyalgia compared to arthritis and healthy people, and positively relate to pain intensity.**	**European Journal of Pain.** 23(3), pp.483–494. IF: 3.188	**Study:** • Contributed to the quantitative analysis strategy and the interpretation of the findings **Paper:** • Wrote the methodology section and commented on the overall manuscript • Responded to the reviewers' comments regarding the methodology

3.3.0 Background

Publication 3 evidences how I extended my understanding of complex scientific knowledge and used intellectual insight to contribute to the generation of a new hypothesis about the mechanism of chronic pain. The research was a collaboration between a research team at the University of Laval, Quebec, Canada and colleagues at UWE. This was my first experience of interrogating primary data whilst working across international boundaries.

This study formed part of a larger, multi- centre, cross-sectional observational study (Appendix 1, publication 3, section 2.1). University ethical approval was obtained prior to my involvement in the study. I was invited to join the study team after data collection was completed which required me to very quickly familiarise myself with the study design and dataset. This was also an opportunity for me to broaden my quantitative research experience. I had previously undertaken analysis of quantitative secondary data during my MRes, however this study enabled me to contribute to the analysis strategy when interrogating and reporting primary data. A quantitative methodology was appropriate in this experimental study in order to measure the variables objectively and apply inferential statistical methods to test a hypothesis (Parahoo, 2014).

Publication 3 explored why people with chronic pain are more vulnerable to experiencing new sensory and motor signs and symptoms when exposed to

sensorimotor conflict, than those without pain. Sensorimotor conflict is another term for sensorimotor incongruence discussed in Chapter 2 (p.22). Previous literature has hypothesised that the presence of a sensorimotor conflict may contribute to pain and other sensory disturbances in chronic pain pathologies for example, phantom limb pain (Harris, 1999). Published evidence demonstrates how sensorimotor conflict also occurred in other chronic pain conditions associated with altered body perception (Hotta *et al*. 2015). An example of this is in CRPS, where altered body perception is evident in patient's reports of the sensation of a distorted limb, in terms of size and shape (Peltz *et al.* 2011). These alterations of body perception are positively related to pain intensity (Valenzuela- Moguillansky, 2013; Lewis & Schweinhardt, 2012).

Publication 3 was built on a prior systematic literature review which concluded that, when sensorimotor incongruence is induced, there are more frequent and intense sensory disturbances in people experiencing chronic musculoskeletal pain than those without chronic pain (Don *et al*. 2017). Due to the heterogeneity across the populations, and the inconsistency of pain outcome measures used, Don *et al*. (2017) were unable to elucidate on the relationship between sensorimotor incongruence and pain. They suggested that further research was needed to investigate this association. Publication 3 was designed to further understand the possible mechanisms underlying this relationship.

On joining the research team, I ensured that I was familiar with the most recent literature reporting sensory disturbance in chronic pain at that time (Boesch *et al.* 2016; Hotta *et al*. 2015; Valenzuela- Moguillansky, 2013; Lewis & Schweinhardt, 2012; Peltz *et al.* 2011). This presented an opportunity to extend my subject knowledge and gain a better understanding of theories underpinning this work.

3.3.1 Data analysis

Data analysis initially focused on between groups comparisons (congruent and incongruent sensorimotor feedback). The statistical analysis was conducted in stages by the lead researcher (CB). Each stage was then reviewed by me, and two other researchers, and used to generate further questions which informed the next step.

Firstly, an analysis of variance (ANOVA) was performed to assess difference between the four groups (Pallant, 2016) (pub 3, section 2.6.1). An analysis of

covariance (ANCOVA) was then conducted to investigate the effect of group, pain intensity and visual feedback (VF) on the total score of sensory disturbances. ANCOVA allowed investigation of the differences between these groups while statistically controlling for an additional variable, in this instance, pain intensity (Pallant, 2016) (Appendix 1, publication 3, section 2.6.2).

Another statistical approach to investigating a large set of variables is principal component analysis (PCA). This is a data reduction technique applied to a large set of variables, in order to produce a smaller, more manageable set of linear combinations of the original variables (Pallant, 2016; Bowling, 2014). PCA was appropriate for this study as it allowed us to take a large set of variables (the conflict-induced sensory disturbances) and investigate if these could be grouped into smaller sets of related items. The PCA strategy was agreed via a series of Skype meetings between three co-authors and I. In order to contribute affectively to these discussions and make sense of complex information, I revisited my quantitative MRes module resources to ensure that I understood the proposed analytical approach. I was not confident in this methodology and, in particular, PCA was unfamiliar to me.

Firstly, data were analysed using Bartlett's test and the Kaiser Maier- Olkin index to ensure the correlation matrix was appropriate to perform a PCA (pub 3, section 2.6.4). I learned that Bartlett's test had to be significant and KMO ≥ 0.60 to perform the PCA.

Subsequent stages included scree plots. These determined the point at which to retain factors, which explained data variance, for further analysis (Pallant, 2016). Finally, a PCA was performed on data collected during the incongruent VF condition stage of the experiment using the nine items of the sensory disturbances questionnaire (Foell *et al.* 2013; McCabe, Cohen and Blake, 2007; McCabe *et al.* 2005). This enabled us to determine whether it was possible to identify subgroups of related items (see below, 3.3.2) within the data. Analyses were only performed on the incongruent VF condition as it induced more sensory disturbances than the congruent VF condition in all groups.

This staged process taught me the importance of considering the results of early data analysis in order to develop a rationale to inform the selection of additional statistical tests. I was able to draw on the expertise of my co-authors to support my

learning and I found the staged analytical approach we adopted very helpful in enabling me to make sense of complex analyses. My quantitative analytical skills significantly improved in contributing to this study. The supportive learning environment afforded by the research team, made me more confident when undertaking quantitative analysis in the future (publication 8).

This was my first experience of interpreting and reporting primary data in collaboration with international colleagues. Devising pragmatic ways of working, despite the geographical and time-zone challenges, was key to its success. Time frames were agreed in order for individual contributions to be completed. Video computer conferencing enabled the team to discuss analysis strategies and interpretation of the findings.

3.3.2 New knowledge

This study is significant in the field of chronic pain as it generated a new hypothesis that pre-existing chronic pain lowers the threshold for the detection of sensorimotor conflicts (Table 3.4, p.46). This is an important finding as it contrasts with existing theory proposing that it is the sensorimotor conflict itself which triggers the painful sensation (Harris, 1999). Our findings also support previous work which categorised sensorimotor conflict into two distinct mechanisms (Nishigami *et al.* 2014). We found new sensations could be categorised into two different groups: (1) participants reported new pain, discomfort, changes to the temperature and weight of the limb, and the sense of losing a limb (2) feelings of peculiarity and the perception of an extra limb (publication 7, discussion, para 3).

On completion of this work, my collaborating co-authors have continued to work in this area and their most recent work will be considered in Chapter 4.

Table 3.4: New knowledge generated from Publication 3

New knowledge generated	• A new hypothesis that pain lowers the threshold for the detection of sensorimotor conflicts, a phenomenon that could contribute to the maintenance of pain in clinical populations
	• Sensory disturbances were found to be strongly related to the intensity of pain, regardless of the pathology
	• The presence of pain did not make people more prone to feelings of peculiarity and the perception of having an extra limb during sensorimotor conflict
	• Two subgroups of conflict- induced sensory disturbances were identified. This suggested that sensory disturbances are potentially related to two different processes and should be considered separately

Publication 3 adds to existing research on persistent pain mechanisms. It may have implications for future targeted treatments and ultimately may improve patient outcomes.

3.3.3 The publication

My contribution to preparing the publication included writing the methodology section and commenting on the manuscript as a whole. In addition, I responded to specific reviewers' comments in relation to the methodology.

3.3.4 RDF domains achieved

Seven RDF sub-domains were achieved whilst undertaking the research presented in Publication 3 (Table 3.5, p.47).

Table 3.5: RDF sub-domains achieved in Publication 3

RDF Sub-domain achieved	Descriptor
A1: Knowledge base	Subject knowledge
	Academic literacy and numeracy
	Information literacy and management
	Research methods – theoretical knowledge
	Research methods – practical application
A2: Cognitive abilities	Analysing
	Synthesising*
	Critical thinking
	Problem solving
A3: Creativity	Inquiring mind
	Intellectual insight
B2: Self-management	Preparation and prioritisation
B3: Professional and career development	Networking
D1: Working with others	Collaboration
	Team working
D2: Communication and dissemination	Publication
	Communication media

***** Descriptors in bold are newly acquired as a result of this publication

3.4 Publication 4

Publication	Journal and Impact Factor	My contribution
Grieve, S., Adams, J. and McCabe, C. (2016a) **"What I really needed was the truth". Exploring the information needs of people with CRPS.**	**Musculoskeletal Care**. 14(1), pp. 15-25. IF:1.92	**Study:** • Principal Investigator, responsible for overall study design, delivery and management • Designed the protocol and study documents (consent, PIS etc.) • Responsible for ethics application, submission and amendments • Received Informed consent from participants • Conducted study recruitment • Organised and conducted the interviews • Typed the transcripts and analysed qualitative data • Presented findings at conferences as poster and an oral presentation **Paper:** • First author • Wrote first draft and subsequent drafts • Submitted paper and responded to reviewers' comments

3.4.0 Background

Publication 4 presents a qualitative study which explores the information needs of people with CRPS from their own perspective. The research was undertaken as part of a MRes Clinical Research and demonstrates my increasing competence as a researcher. This was my first experience as a Principal Investigator (PI) and I led all aspects of the design, delivery and management of the study. I nevertheless benefited from the support of my supervisory team to ensure the research was methodologically robust and conducted with integrity.

The research question was informed by my clinical experience of patients reporting difficulty in finding reputable information from sources that were relevant to them, for example, accessing guidance on how to self-manage their condition in a UK healthcare setting. At this time, and currently, UK clinical guidelines

emphasised the responsibility of health professionals to support patients by providing comprehensive information about CRPS (Goebel, Barker and Turner-Stokes *et al*. 2012). Following the process recommended by the Critical Appraisal Skills Programme (CASP, 2018), I conducted a systematic literature review. This confirmed there was little evidence about what information was needed by individuals with CRPS, indicating a need for further work in this area. At the time of this research, it was not possible to accurately predict the outcome of CRPS, and this remains the case today. Evidence-based information continues to be crucial to enable an individual to adopt self-management strategies that will give them the best chance of rehabilitation and optimised quality of life (Goebel *et al*. 2019). My aim was to identify what information individuals felt was most relevant to enable them to engage with rehabilitation, and how they would like to access this information.

3.4.1 Methodology

This research was my first experience of using a qualitative methodology and was an opportunity to develop new skills and competence in the analysis and interpretation of qualitative data. A Masters module, ‘Applied research methods in qualitative research’, had equipped me with the knowledge to select an appropriate design which sat within my philosophical position of phenomenology; a stance from which to explore an individual's lived experience, identifying issues which are important to them and offering insights into their world (Moule, 2015; Parahoo, 2014; Barbour, 2009).

3.4.2 Patient and public involvement in research

This study was one of my first experiences of patient and public involvement in research (PPI). This is defined as research 'with' or 'by' patients/public as research partners rather than as a participant in a research study (INVOLVE, 2012). PPI is increasingly required by funders and research organisations and is considered best practice when designing and delivering research (Boylan *et al*. 2019). Examples of PPI include patient/public membership of study steering groups, contributing to the development of research documentation, and as co-applicants on research funding applications (INVOLVE 2012). The evidence suggests that PPI can lead to increased quality and relevance of research through the experiential knowledge and personal insight that service users can bring to a study

(Smith, Bélisle-Pipon and Resnik, 2019; Brett *et al*. 2014). I chose to involve patients from the early stages of the design by confirming with them that the aims of the study were pertinent to their experience. This consultation process was undertaken informally within the clinical setting. On reflection, the study would have benefited from further patient involvement at later stages, for example, when I was developing the interview guide. When this study was conceived I was less aware of the mechanisms for patient and public involvement (PPI) in research. However, I will demonstrate my increasing understanding and utilisation of PPI later in this thesis (3.6.3, p.65)

3.4.3 Ethical approval

With the support of my supervisory team, I designed the study protocol and obtained university ethical approval appropriate for people recruited outside of an NHS organisation (HRA, 2019). This was my first experience of submitting an ethics application and it made me acutely aware of the importance of adhering to the ethical principles which underpin all research, in order to protect and promote the interests of the participant (HRA, 2017; Parahoo, 2014). For example, my clinical experience informed me that interviewing people about their experience of CRPS had the potential to trigger distress, as it may evoke negative feelings, so I defined a process to refer participants for further support if necessary. Ethical considerations when undertaking research are discussed further in section 3.7.3.2 (p.74).

3.4.4 Data collection

I was responsible for the recruitment strategy and learned the challenges of recruitment from a discrete homogenous population. Although face to face interviews were considered, I made the decision to collect data using telephone interviews as it allowed access to individuals over a wide geographic area and did not exclude those unable to travel (Holt, 2010; Musselwhite *et al.* 2007). I recruited CRPS participants via patient-led and professional websites, which potentially provided access to a wide demographic with this uncommon condition (Rodham, McCabe and Blake, 2009; Hamilton and Bowers, 2006). Despite this approach, recruitment of 8 patients took much longer than anticipated. Initially I had sought permission to use two websites, however one went offline during the study due to management issues. Two further websites were identified but recruitment was

delayed, and with fewer responses to the adverts than I had predicted. This experience taught me to adopt a broad recruitment strategy from the outset without over reliance on one method. In hindsight, this could have included study adverts on social media, capitalising on cost-effective ways that people with shared health conditions connect (Ryan 2013; Farmer *et al*. 2012).

This study presented new opportunities for my research skills development and included; designing the study documents, acquiring interviewing techniques, transcribing skills and undertaking thematic analysis. Prior to participant recruitment I undertook a two day training course to learn to use QSR International's data management software 'NVivo', which taught me how to subsequently code and manage the volume of data generated from the eight transcripts. This is a skill that I have since taken forward in other studies (Publication 7). However, this was, at the time, my first experience of thematic analysis outside of a classroom and I discovered that, whilst the software was useful for the coding process, I performed better with a tactile approach to finding patterns and themes within the dataset, using paper and scissors to map these across the bedroom floor.

3.4.5 Leadership

In order to deliver the study successfully, I learned to prioritise and manage my time effectively including using a Gantt chart to project the study schedule. As PI, I was required to make decisions on the conduct of the study which sometimes took me outside of my comfort zone, for example in relation to the recruitment strategy. This experience encouraged me to seek formal leadership training to increase my confidence and problem-solving ability and I gained a competitive place on the NHS Frontline leadership course for nurses and midwives in 2015 (3.6.2, p.63).

3.4.6 New knowledge

The findings presented in Publication 4 provided a unique insight into what information is needed to enable CRPS patients to engage effectively with rehabilitation interventions (Table 3.6, p.52). As a researcher embedded within clinical care, I was able to quickly implement the findings into practice by collating a patient information package and providing patients with a link to specialist services by geographic area via the CRPS Network website (http://www.crpsnetworkuk.org/). More recently Publication 4 has informed a

subsequent study investigating the online educational resources which are available for people living with CRPS. Under my supervision, this further work was conducted by an undergraduate nursing student on a Versus Arthritis internship with our service and was presented as a selected showcase poster at the British Society of Rheumatology annual conference (Fry *et al*. 2019). I have recently been contacted by a postgraduate student who intends to build on Publication 4 and has sought my input to develop their research question.

Table 3.6: New knowledge generated from Publication 4

New knowledge generated	• There was a gap between what information was needed by a person with CRPS and what information they were able to access
	• There was a reported lack of appropriate and timely information available for those with CRPS

3.4.7 The publication

This paper was my first opportunity to report a research study as lead author. I selected the journal 'Musculoskeletal Care' (Wiley) as CRPS sits within this specialism. I was familiar with this journal, and it routinely publishes qualitative research. I was responsible for writing the first draft, responding to my co-authors' feedback and submitting the manuscript. I responded to the reviewers' comments which included providing clarification on patient involvement in the study and data collection strategies.

Publication 4 taught me how to ensure the quality of qualitative research and how this is different from quantitative studies. Qualitative research cannot be judged on reliability, as the researcher inevitably influences the process and can be seen to introduce bias (Appendix 1, publication 4, limitations, p23) (Braun and Clarke, 2013). However, the use of direct quotes within the publication, including detail of context and traceability to the original anonymised source improves credibility, enabling the reader to assess the interpretation offered by the researcher (Braun and Clarke, 2013; Green and Thorogood, 2011).

As a result of this research, I was invited to give my first oral platform presentation at a CRPS International Scientific and Clinical Meeting (Grieve, Adams and

McCabe, 2013). I also presented a poster reporting the findings at the British Pain Society Annual Scientific Meeting in 2014 (Grieve, Adams and McCabe, 2014).

3.4.8 RDF domains achieved

Eleven RDF sub-domains were achieved whilst undertaking the research presented in Publication 4 (Table 3.7).

Table 3.7: RDF sub-domains achieved in Publication 4

RDF Sub-domain achieved	Descriptor
A1: Knowledge base	Subject knowledge
	Research methods – theoretical knowledge
	Research methods – practical application
	Information seeking
	Information literacy and management
	Academic literacy and numeracy
A2: Cognitive abilities	Analysing
	Synthesising
	Critical thinking
	Evaluating*
A3: Creativity	Inquiring mind
	Intellectual insight
B1: Personal qualities	**Responsibility**
	Enthusiasm
	Integrity
	Perseverance
	Self-confidence
	Self-reflection
B2: Self-management	Preparation and prioritisation
	Time management
B3: Professional and career development	Networking
	Reputation and esteem
C1: Professional conduct	Ethics, principles and sustainability
	Health and safety
	Legal requirements
	IPR and copyright
	Respect and confidentiality
	Appropriate practice
	Attribution and co-author
C2: Research management	**Risk management**
	Project planning and delivery
D1: Working with others	Team working
	Mentoring
	Supervision
D2: Communication and dissemination	Publication
	Communication methods
D3: Engagement and impact	**Public engagement**

***** Descriptors in bold are newly acquired as a result of this publication

3.5 Publication 5

Publication	Journal and Impact Factor	My contribution
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, pp. 331–340. IF: 3.188	**Study:** • Designed the research question and protocol • Defined the search strategy • Conducted the systematic literature review • Led data analysis • Reviewed a subset of the data with a co-researcher at a later stage of the data analysis due to volume of results • Presented poster at national conference • Oral presentation at an international meeting of CRPS experts **Paper:** • First author • Wrote first draft and revised subsequent drafts • Submitted paper and responded to reviewers' comments, resubmitted

3.5.0 Background

Publication 5 presents a systematic literature review (SLR) which was the first to identify the patient or health professional reported questionnaire outcome measures used in CRPS clinical trials between 2000-2014.

As a clinical researcher, I was aware of the methodological challenges associated with the synthesis of CRPS research evidence. Incidence rates of CRPS are low (de Mos *et al*. 2007) and research was, and is, confined to small study populations. Multicentre collaborative research was needed to achieve sufficient sample sizes for meaningful studies however, this was hampered by the wide range of different outcome measures used to capture the multidimensional nature of CRPS. At the time of Publication 5, the absence of an international, standardised, set of CRPS outcome measures meant it was impossible to answer key questions on CRPS by comparing data across clinical studies and countries. This impeded the synthesis of clinical research evidence and limited its translation to global clinical practice (Boers *et al.* 2014; Macefield *et al*. 2014).

To address this issue, an international consortium was established in 2013 to agree upon a minimum core set of health-related questionnaire outcome

measures recommended for use in all future CRPS clinical studies (Publication 6). This initiative was conceived by the CRPS clinical research lead at the RUH with the ultimate aim of establishing an international CRPS clinical research registry (thesis p.65); agreeing a core set of outcome measures was the first step. The consortium currently comprises clinicians, researchers, patients and industry partners from 20 countries.

3.5.1 My role in conducting the SLR

My track record of successfully delivering CRPS research studies, and experience as PI of Publication 4, culminated in my role as co-lead of this research study, which was given the acronym 'COMPACT': Core Outcome Measures for complex regional PAin syndrome Clinical Trials. At the first international COMPACT workshop (3.6.2, p.63) it became apparent that in order to agree a CRPS core outcome measurement set (COMS), we firstly needed to establish, via an SLR, what patient-reported and health professional-reported questionnaire outcome measures were currently used in CRPS clinical studies. The findings would then inform the decision-making process.

A COMS 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). The set of outcomes should comprise the minimum number of domains needed to answer the proposed research question; be appropriate for the population under investigation, and measure positive and negative outcomes (Turk *et al.* 2003). Each domain should be represented by a valid and reliable measurement tool, such as a patient-reported questionnaire or a clinical measure.

As co-lead I undertook the SLR on behalf of the COMPACT consortium, having acquired the skills to do so through my BSc and MRes modules. I gained confidence in organising a team of researchers (see below) in order to complete the work with the aim to present the results at an international meeting.

When conducting a SLR, a defined process should be followed to ensure that the results can be reproduced and verified (Polit and Beck, 2017). Firstly, I defined the inclusion and exclusion criteria to ensure that the relevant papers were systematically identified and evaluated (Parahoo, 2014; Bettany-Saltikov, 2012). I needed to ensure I included the wide range of terms for both intervention studies

and CRPS (Todorova *et al*. 2013). To address the former, I used a Cochrane systematic review of intervention studies to inform my search terms (O'Connell *et al*. 2013) and confirmed these with my study co-lead and a colleague at UWE.

I conducted the search of primary data independently and appraised the evidence in order to identify the relevant papers. For comprehensiveness, five databases were searched resulting in 1326 papers to which the inclusion and exclusion criteria were applied to the title and abstract. This was time consuming and, as the SLR was time-limited, I used my PROactive network to identify a UWE research associate who assisted me in the final stages (Appendix 1, publication 5, section 2.2, para 2). Leading the SLR taught me the importance of a methodical approach to managing a high number of search results. I used Clarivate Analytic's 'EndNote' reference management software to facilitate the process.

There are a number of critical appraisal tools available (CASP, 2019; Greenhalgh, 2014) which can help the researcher systematically assess and interpret evidence in order to consider its validity, results and relevance to their context (Gerrish and Lacey, 2010). However, I made the decision not to assess the quality of the 104 papers included, as it was the measures used in the various studies which were of interest, rather than the validity and reliability of the individual findings.

3.5.2 New knowledge

The findings of this review confirmed that the complex nature of CRPS has led researchers to use a wide range of questionnaires to measure patient outcomes. Compared to the findings of an earlier literature review (Schasfoort *et al.* 2000), there was clear evidence of a shift over time from outcomes measures related to sensory, motor, trophic and autonomic impairment towards studies using health outcomes related to physical functioning in the context of rehabilitation medicine (Appendix 1, publication 5, section 4, para 1). A change in CRPS diagnostic criteria may account for this, as the current criteria have a stronger emphasis on motor function which may have encouraged a greater focus on the assessment of physical function in studies conducted after 2000 (Harden *et al*. 2010).

This work informed the novel development of patient-reported COMS to be recommended for use in all CRPS clinical studies (Table 3.8, p.57).

Table 3.8: New knowledge generated from Publication 5

New knowledge generated	• Patient or health professional-reported questionnaire outcome measures, used in CRPS clinical trials between 2000-2014, were identified
	• Patient or health professional-reported questionnaire outcome measures, which had been developed specifically for use in CRPS populations, were identified
	• A shift towards using health outcomes related to daily functioning in the field of CRPS since 1998 was identified

Leading this work provided an excellent basis from which to move the COMPACT study forward. I was equipped with an in-depth knowledge of the questionnaire outcome measures used in CRPS research studies and how they were applied so I was able to model potential COMS based on this work (Publication 6).

3.5.3 The publication

This SLR supported the early stages of an international research study and so it was appropriate to submit the manuscript to an international publication. The European Journal of Pain) was selected as it had an impact factor (IF) of 3.188, and therefore reached a wide audience. The IF reflects the number of citations articles in a journal have received within in a specific time (Web of Science, 2020). I drafted the manuscript, collated feedback from my co-authors and was responsible for the submission and for satisfactorily addressing reviewers' comments. This publication comprised the main manuscript and supplementary information providing: the key search terms, a list of the 104 papers included in the SLR and a list of those publications that were not included due to full text versions having been unavailable.

3.5.4 Opportunities as a result of this publication

I presented the SLR findings to members of the CRPS International Research Consortium at a meeting in Chicago, and as a poster at the British Pain Society

Annual Scientific Meeting in 2015, where it was awarded one of the best submitted posters (Grieve *et al.* 2015b) (Appendix 5).

The Chicago meeting was my first oral presentation to an international audience and this experience significantly improved my confidence in public speaking. The positive response from colleagues who had many years of expertise, validated my work and gave me the confidence to move forward with the COMPACT study (publication 6). The next step was to build on this work and co-lead the international research study presented in publication 6.

3.5.5 RDF domains achieved

Nine RDF sub-domains were achieved whilst undertaking the SLR presented in Publication 5 (Table 3.9).

Table 3.9: RDF sub-domains achieved in Publication 5

RDF Sub-domain achieved	Descriptor
A1: Knowledge base	Subject knowledge
	Research methods – theoretical knowledge
	Research methods – practical application
	Information seeking
	Information literacy and management
	Academic literacy and numeracy
A2: Cognitive abilities	Evaluating
B1: Personal qualities	Responsibility
	Perseverance
	Integrity
B2: Self-management	Preparation and prioritisation
	Time management
	Commitment to research*
B3: Professional and career development	Networking
	Reputation and esteem
C1: Professional conduct	Health and safety
	IPR and copyright
	Respect and confidentiality
	Attribution and co-author
	Appropriate practice
C2: Research management	Project planning and delivery
D1: Working with others	Team working
D2: Communication and dissemination	Publication
	Communication methods

***** Descriptor in bold is newly acquired as a result of this publication

3.6 Publication 6

Publication	Journal and Impact Factor	My contribution
Grieve, S., Perez, R.S.G.M., Birklein, F., Brunner, F., Bruehl, S., Harden, R.N., Packham, T., Gobeil, F., Haigh, R., Holly, J., Terkelsen, A., Davies, L., Lewis, J., Thomassen, I., Connett, R., Worth., T, Vatine, J-J. and McCabe, C.S. (2017c) **Recommendations for a first Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies (COMPACT).**	**Pain** 158(6), pp.1083-1090. IF: 6.029	**Study:** • Overall project co-lead • Contributed to study design • Reviewed the relevant literature • Co-ordinated and delivered this international project including liaison with international experts in the field of CRPS • Co-ordinated and co-chaired the international workshops • Prepared funding application • Oversight of study budget and timeline • Modelled potential core measurement sets • Co-led and contributed to the work defining and agreeing the CRPS questionnaire core measurement set • Sought approvals to use the defined outcome measures from the authors/distributors • Organised and led focus groups • Led patient involvement activities • Presented posters and oral session at national and international conferences **Paper:** • First author • Wrote first draft and revised subsequent drafts • Submitted paper and responded to reviewers' comments

3.6.0 Background

Publication 6 comprises a narrative report of an international research study which developed and agreed the first questionnaire core outcome measurement set (COMS) for CRPS clinical studies. The study and the resultant COMS are known by the acronym COMPACT. The research reported here was the next stage of the COMPACT initiative that was first described in Publication 5 (p.54). The length of this commentary reflects the impact this research had on my development as an independent researcher. Publication 6, in particular, will demonstrate my ability to conceptualise, design and implement a study for the generation of new knowledge at the forefront of the field of CRPS.

This was my first experience of co-leading an international study and required me to be able to effectively manage multiple work streams. At the time of study inception, I had just completed my MRes and had experience as a Principal Investigator (Publication 4). I was able to apply this skill set to the COMPACT study and I was responsible for co-leading all aspects of this work. Although there were no research participants, I adopted the ethical approach of a similar initiative facilitating the development of COMS's (Prinsen *et al.* 2016) and obtained university ethical approval.

Co-leading this study enabled me to build significant expertise around patient-reported outcome measures and their application to international registries in the field of chronic pain. My first responsibility was to conduct an in-depth review of the existing literature to identify an appropriate methodology for developing a COMS; specifically exploring initiatives reporting the development of COMS in chronic pain and rheumatology (Boers *et al.* 2014; Dworkin *et al*. 2005; Fried, Boers and Baker, 1993).

3.6.1 Methodology

The first methodology I considered was Core Outcome Measures in Effectiveness Trials which create COMS's for a broad range of trial populations by identifying the relevant outcome measures for the condition and then determining which of these were core (Prinsen *et al.* 2016). This methodology was not adopted as, to answer the specific COMPACT research question, the members of COMPACT concurred it was necessary to agree the core domains relevant to CRPS first, and then identify which outcome measures best captured these.

I then considered the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Turk *et al.* 2003). Adopting a consensus approach, IMMPACT recommend six core domains are used in chronic pain clinical trials (Turk *et al.* 2003) (Table 3.10, p.62). IMMPACT recommend using specific outcome measures within each domain of interest (Dworkin *et al*. 2005), for example, using the Short-Form McGill Pain Questionnaire to measure the sensory and affective qualities of pain (Melzack, 1987) and the Short Form-36, as a generic measure of physical functioning (Ware and Sherbourne, 1992). Using specific measures in all chronic pain clinical trials would address the variability in outcome measures and facilitate the pooling and comparison of data. I considered

using these core domains however, further investigation indicated they were not specific enough for a condition with the complexity and multifactorial nature of CRPS (Dworkin *et al*. 2005). Email correspondence with Professor Dennis Turk, one of the Directors of IMMPACT, endorsed the methodology of the COMPACT work and agreed CRPS-specific domains would be more appropriate.

The third methodology considered was that of 'Outcome Measures in Rheumatology' (OMERACT); an international initiative to improve outcome measurement in rheumatology. This had successfully achieved consensus on COMS's in a number of rheumatology conditions (Tugwell *et al*. 2007). At the first international COMPACT workshop (Appendix 1, publication 6, 2.3.3), I proposed we adopt the OMERACT methodology outright. However, this was challenged by some COMPACT members because they felt the domains defined by OMERACT (Table 3.10, p.62) did not encompass the full scope of those measured in chronic pain conditions by IMMPACT (Dworkin *et al.* 2005). This lack of agreement had the potential to change our methodology. However, rather than overruling this, I, and my co-lead, facilitated a further discussion which concluded that we should follow the advice of our COMPACT members, which was to adapt the IMMPACT domains for COMPACT (Turk *et al.* 2003), and to define CRPS-specific domains (Table 3.10, p.62).

I learnt that a key aspect of leading the study was reaching an agreement the entire group could support and feel comfortable with. Therefore, to ensure that every member of COMPACT had a voice throughout the decision-making process, I maintained the consensus approach used by the OMERACT initiative, even though we were not adopting the OMERACT methodology outright (Tugwell *et al*. 2007). This taught me how leadership is about being adaptable; modifying my approach in response to changing circumstances.

Once the COMPACT methodology and domains were agreed, the next step was to achieve consensus regarding the questionnaire outcome measures to be included in the COMS, and that would represent the agreed domains (Tugwell *et al*. 2007).

Table 3.10: Core domains: comparison across methodologies

	IMMPACT core domains for chronic pain clinical trials (Turk *et al.* 2003)		**OMERACT core domains (Boers *et al.* 2014)**		**Outcome measures included in COMPACT (Grieve *et al.* 2017c)**
				1	Participant characteristics
1	Pain	1	Life impact (eg. symptom and functional domains)	2	Pain
2	Physical functioning			3	Participation and physical function.
3	Emotional functioning			4	Emotional and psychological function
4	Participant ratings of improvement and satisfaction with treatment	2	Resource Use/ Economical impact (societal cost)	5	Patient's global impression of change
5	Symptoms and adverse events	3	Pathophysiological Manifestations (biological and physiological)	6	Disease Severity
6	Participant disposition	4	Death (cause and mortality)	7	Catastrophising
				8	Self-efficacy

An example of how this consensus method applied in practice, was the selection of the SF-McGill Pain Questionnaire-2 (SF-MPQ-2) by the COMPACT group. The SF-MPQ-2 comprises four subscales representing pain qualities; one of which consists of six neuropathic pain descriptors (Dworkin *et al*. 2009). COMPACT was designed to use the minimum number of questions possible, to reduce patient burden in questionnaire completion, and so use of the entire SF-MPQ-2 exceeded this objective. Through consensus, it was agreed we should use the neuropathic qualities sub-scale as a stand-alone measure. Rasch analysis was conducted by one of the COMPACT group members to reduce the number of questions contained within the SF-MPQ-2. This statistical model uses probability to predict the likelihood of a person getting a correct response for any given scale item, allowing researchers to adapt measurement instruments (Pallant, 2016). Our publication, of which I was a co-author, endorsed the use of this sub-scale however, we recommend that our analysis is repeated with a larger sample (Packham *et al*. 2018).

3.6.2 Leadership of COMPACT

The COMPACT study included 4 international workshops comprising clinicians, researchers, patients and industry partners, bringing a range of perspectives. I ensured that the workshops were accessible from cultural, language and lay perspectives, a skill which I honed as the study progressed. Specific people management skills were needed, as the diverse range of disciplines and clinical interests meant that the international research team initially had different priorities in relation to developing a COMS. Attending the Frontline leadership programme for nurses and midwives in 2015 introduced me to the healthcare leadership model and how personal qualities such as self-awareness, self-confidence and resilience, are at the foundation of our behaviour as leaders (NHS Leadership Academy, 2013). I gained an understanding of team dynamics and how to widen my circle of influence (Covey, 2015). This equipped me to co-chair the COMPACT international workshops and co-ordinate and deliver the supplementary work, with my confidence increasing exponentially. As co-lead, I planned the agenda, designed PowerPoint presentations, prepared and oversaw the group work, led the consensus process and recorded the outcome (Appendix 1, publication 6, 2.3.1).

Achieving consensus on the outcome measures to be included in the COMS presented a significant challenge. Leadership and mediation skills were needed to achieve a meaningful vote. To facilitate this, I divided the consensus process into steps; (1) presenting the proposed options to the entire group (2) facilitating discussions within smaller groups (3) overseeing and recording the vote (Appendix 1, publication 6, 2.3.6).

Once the patient-reported outcome measures were agreed (Appendix 1, publication 6, 2.3.4), I was responsible for obtaining permission from the authors or distributors of each questionnaire for its use within COMPACT. This required diligence. I learned to communicate the meaning of a COMS to those less familiar with this construct, which required confidence and in-depth knowledge. This was a significant piece of work and I ensured the study was compliant with licensing requirements and fit for purpose in the long-term.

In the early stages of this work, I developed a collaboration with a Swiss Consultant Rheumatologist who had published widely in the CRPS field and had previously collaborated with the Bath research team (Llewellyn *et al*. 2018). This was particularly gratifying for me as his publications included a key paper that informed my MRes research question (Brunner *et al*. 2010). I was a co-applicant on a successful grant application to a clinical foundation in Switzerland which funded the study reported in Publication 6. I prepared the funding application, timeline and budget; managing the latter throughout the study. I learnt that shared research aims, prioritising and setting expectations were essential in order to ensure the study's aims and objectives were met within the agreed timeframe.

3.6.3 Communication

Effective collaboration with COMPACT members underpinned this study. It enabled researchers from across disciplines to share their knowledge to address complex problems (Chan, 2015) and required high level leadership skills. The study required leading a team of international experts, and I was mindful of cultural and language considerations. COMPACT members had different levels of expertise in the field of CRPS and so I needed to ensure presentations were designed to hold the attention of a wide audience. This study demonstrates how I can confidently communicate to a range of audiences and inspire the commitment of the research team to the long term aims. In addition, I developed an

international network of contacts within my field, which is still growing. Future work will consider using video conferencing software to further improve communication across the group.

Involvement of patient partners (thesis p.49) in this study was essential to ensure the COMS included measures that were important to people with CRPS and pertinent to their experience of CRPS (Nelson *et al.* 2016; Turk *et al*. 2008). The evidence base for measuring the value of PPI is not yet established but to ensure the involvement and contribution of our patient researchers had an impact, I involved them as equal partners at every stage; from study design to co-authoring the publication (Boylan *et al*. 2019; Staley, 2015). I facilitated their involvement to adhere to best practice recommendations including ensuring their role was clearly defined and appropriate support was provided (INVOLVE, 2012). As the named contact for our patient partners, I was able to provide additional information or clarification on request. I ensured we continually gained their perspective so the final COMS was embedded in the patient experience (de Wit *et al.* 2013; Staniszewska *et al.* 2012). For example, I organised and led two focus groups to collate feedback on the draft COMPACT questionnaire prior to this being presented at a workshop. The focus groups comprised UK patient partners for convenience however, feedback from international patient partners was sought at a subsequent workshop. Patient feedback enabled me to make significant changes to the layout of the final document in relation to more accessible formatting.

3.6.4 New knowledge

Publication 6 generated new knowledge (Table 3.11, p.66) which underpins the building of an international clinical research registry for CRPS. This work is ongoing and will address the challenge of synthesising large international clinical research data sets to facilitate a better understanding of the mechanisms of CRPS and potential therapeutic interventions. This work may provide a model for future, similar initiatives in other health conditions. The methodology used in Publication 6 also informed a Delphi study to define internationally agreed core *clinical* outcome measures for CRPS clinical research studies. These will also be an integral part of the international CRPS registry (Llewellyn *et al.* 2019)

Table 3.11: New knowledge generated from Publication 6

New knowledge generated	• The first questionnaire COMS for CRPS clinical studies was agreed by an iterative process of consensus.
	• A novel method of collecting standardised CRPS outcome data was developed.
	• The first published recommendations for the collection of CRPS outcome data in international research practice.

3.6.5 The publication

To facilitate the international impact of the COMPACT study, I selected the journal PAIN (IASP) for the submission of Publication 6. With an IF of 6.029, it has a worldwide audience. I prepared the first draft of the manuscript, and revised this in response to comments from co-authors. Two patient researcher partners co-authored this paper and I was responsible for ensuring they had a clear understanding of the process and could contribute as equal team members. I submitted the manuscript and responded to reviewers' feedback after consultation with my co-authors. I checked the proofs prior to publication. This process required attention to detail.

3.6.6 Opportunities presented from this research

A considerable number of opportunities have been presented to me as a result of Publication 6. First authorship and co-leading this work has raised my profile as a researcher within the field of CRPS. It stimulated an invitation to present at my first international conference of the IASP CRPS Special Interest Group in Zurich (2015). At the British Pain Society Annual Scientific Meeting in 2016, I presented a poster (Grieve *et al.* 2016c) and was invited to present and be a member of a panel for a parallel session. Other panel members included 3 eminent Professors specialising in Chronic Pain. This experience validated my position as a leader in this field and, although I initially did not feel confident, I used this to identify areas for development, such as responding to delegates' questions.

I presented an overview of the COMPACT study at the IASP CRPS Special Interest Group at the 16th World Congress on Pain in Japan and presented a poster at the main conference (Grieve *et al.* 2016d). I presented a poster at the IASP CRPS Special Interest Group in Cork, Ireland (Grieve *et al.* 2017b). As a result of my experience working with patient partners, I was invited to give a presentation entitled 'How to do it: Professional experience of working with patients as research partners', at the British Pain Society Annual Scientific meeting in May 2019.

As a result of Publication 6, I was invited to write a lay-friendly blog post for the website Body In Mind https://bodyinmind.org/?s=grieve.This website has a wide social media reach in the field of clinical pain sciences, further raising my profile as a pain researcher. I have also been invited to join the editorial board of the journal Pain Medicine which I will pursue when my DPhil is completed.

Future work proposed in Publication 6 included a survey of international researchers to identify the outcome measures they currently use in CRPS clinical trials. This survey is now completed and was reported at the British Pain Society conference (Grieve *et al.* 2017a). The survey will be repeated after the international registry is established to evaluate the international impact of adopting the COMPACT outcome measures. The next steps were to test the practicalities of collecting and managing the COMS data within an international CRPS research population. This work is presented in Publication 7.

3.6.7 RDF domains achieved

All twelve RDF sub-domains were achieved whilst undertaking the research presented in Publication 6 (Table 3.12) and this work has therefore significantly contributed to my development as an independent researcher.

Table 3.12: RDF sub-domains achieved in Publication 6

RDF Sub-domain achieved	Descriptor
A1: Knowledge base	Subject knowledge
	Research methods – theoretical knowledge
	Research methods – practical application
	Information seeking
	Information literacy and management

	Academic literacy and numeracy
A2: Cognitive abilities	Analysing
	Synthesising
	Critical thinking
	Evaluating
	Problem solving
A3: Creativity	Inquiring mind
	Intellectual insight
	Innovation
	Argument construction*
	Intellectual risk
B1: Personal qualities	Responsibility
	Self-reflection
	Enthusiasm
	Perseverance
	Integrity
	Self-confidence
B2: Self-management	**Responsiveness to change**
	Preparation and prioritisation
	Time management
	Commitment to research
	Work-life balance
B3: Professional and career development	Networking
	Reputation and esteem
C1: Professional conduct	Ethics, principles and sustainability
	Health and safety
	Legal requirements
	IPR and copyright
	Respect and confidentiality
	Attribution and co-author
	Appropriate practice
C2: Research management	Project planning and delivery
	Research strategy
C3: Finance, funding and resources	**Income and funding generation**
	Financial management
	Infrastructure and resources
D1: Working with others:	Team working
	Influence and leadership
	Collegiality
	People management
	Collaboration
D2: Communication and dissemination	Communication methods
	Publication
	Communication media
D3: Engagement and impact	Public engagement
	Teaching
	Enterprise
	Policy
	Society and culture
	Global citizenship

***** Descriptors in bold are newly acquired as a result of this publication

3.7 Publication 7

Publication	Journal and Impact Factor	My contribution
Grieve, S., Brunner, F., Buckle, L., Gobeil, F., Hirata, H., Iwasaki, N., Moseley, GL., Sousa, G., Vatine JJ., Vaughan-Spickers, N., Xu, J., McCabe,C (2019) 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.	Musculoskeletal Care. 17(3), pp. 249–256 IF:1.92	Study • Overall project co-lead • Co- designed the protocol • Identified an electronic data management system • Co-designed the research method • Compiled the full protocol • Obtained permission to use the questionnaire outcome measures within the protocol • Prepared funding applications • Registered the protocol Paper: • First author • Wrote first draft and edited feedback from co-authors • Submitted paper

3.7.0 Background

This publication presents the protocol of an observational study which I co-lead. The study is currently in progress and will be discussed further in Chapter 4 (p.95). It is a multicentre, feasibility study to test the feasibility and acceptability of collecting the COMPACT COMS questionnaire data in an international population. The development of the COMS is reported in publication 6 (thesis p.59). Throughout publication 7, the COMS was abridged as the 'COMPACT questionnaire' for ease of communication between researchers. This term will be used throughout this commentary for consistency.

Nine patient-reported outcome measures (PROMs) are included in the COMPACT questionnaire (Appendix 1, publication 7, table 1). In addition, there is one clinician-reported measure, namely the CRPS severity score (Harden *et al.* 2017) (Appendix 1, publication 7, 3.4). The protocol presented in Publication 7 is to test the practicalities around collecting these data, and the findings will inform the processes for the long-term CRPS international clinical research registry.

This commentary will describe how I co-designed the study protocol. Key decisions were shared with the study co-lead via a process of consensus. Although I had experience of designing previous protocols (Publication 4 & 8), publication 7 presented a new challenge due to the complexity presented by an international study.

As co-lead of the COMPACT initiative from inception, I was well-placed to co-design this protocol as I had an in-depth understanding of the work. I selected an observational design as the study aims to test the feasibility and acceptability of the *process* of collecting and managing the COMPACT data, rather than investigating the cause-and-effect relationship between variables using an experimental approach (Gerrish and Lathlean, 2015).

In developing the protocol, international research centres were selected to represent the diversity of countries which may wish to use the COMPACT registry in the future, for example, across continents and using different languages (Appendix 1, publication 7, 3.2). I sought protocol agreement from the Principal Investigators (PI) who would deliver the study internationally.

My role in the protocol design comprised three key work streams: (3.7.1) identifying an appropriate electronic data management system for use in the subsequent study and written into the protocol, (3.7.2) designing the research method and (3.7.3) compiling the full protocol. Each will be addressed separately within this commentary.

3.7.1. Identifying an electronic data management system (EDMS)

The future clinical research registry will comprise a large, international dataset. The co-lead and I considered digital technology the most cost-efficient and secure way of collecting these data in the long-term (Ashley *et al.* 2011: Nelson *et al*. 2016). This aligns with the NHS drive to use digital technology to accelerate the implementation of health research (NIHR, 2019a). The study presented in Publication 7 would test and refine the identified EDMS to ensure it could collect and securely manage the feasibility study data and that of the future registry. This presented a new opportunity for my development and required gaining an in-depth understanding of the key elements of EDMS's relevant to this study (Table 3.13, p.71). From my experience in commercial and academic research, I knew there were a number of potential systems which needed to be explored in order to

inform the design of the protocol. This involved meeting with local and international researchers, who were developing or using EDMS's, to better understand the systems.

Two EDMS's were disregarded due to cost or no track record of international data management (Table 3.13). Building on an existing, collaborative relationship with the Clinical Informatics Research Unit (CIRU) at the University of Southampton, UK , I met with the development team to investigate the use of the ALEA[2] EDMS. The co-lead and I selected this system as it met the project's requirements in terms of functionality (Table 3.13).

Table 3.13: Study requirements of EDMS's and those considered.

Study requirement of EDMS	**Rationale**	**EDMS's considered**		
		Research Electronic Data Capture (REDCap)	**Local UK database**	**ALEA**
Proven track record in clinical trials worldwide	Study requires international data management	✓	X	✓
Secure web application for building and managing online surveys and databases.	To comply with data protection regulations, ethical and legal requirements	✓	✓	✓
Facility to design a bespoke COMPACT platform	To incorporate all the COMPACT-specific questionnaire outcome measures	✓	?	✓
Available in multiple languages	International research centres and their patients' require access in their local language	✓	X	✓
Separate password-protected platform for patients	To enable patients' to complete the questionnaire online if preferred	✓	✓	✓
Development and hosting cost within study budget	Limited budget available	X	Cost not obtained	✓

3.7.2. Designing the study method

The process I followed to design the study method is described in detail in Table 3.14, p.72.

[2]*ALEA means 'dice' in Latin, suggesting things have happened that can't be changed back*

Table 3.14: Designing the study method

Specific method	Key aspects of designing the study method
Study population	As an observational study testing recruitment and data collection processes, a convenience sampling strategy was most appropriate. This provided easy access to a known population (Bowling, 2014): (1) adults with CRPS attending a clinical visit (2) clinicians working in the field of CRPS who were willing to deliver the study and feedback on their experience of doing so. These groups were appropriate as I wished to test the processes within the population who would be using COMPACT documentation, and registry, in the future. A broad inclusion criterion ensured a wide range of patients would be recruited to represent different ages, disease durations, gender, ethnicity and COMPACT access requirements. The size of the sample was determined to enable sufficient data to assess the processes under investigation whilst meeting ethical standards (NIHR, 2019b)
Recruitment	Patients attending the participating study centres would be identified by the local multidisciplinary team as potential recruits to the study. After consultation with my co-lead, I made the decision that recruitment could be at any point in their treatment pathway. The rationale for this was because the purpose of this study was to test the recruitment and data collection *processes* rather than analyse the COMPACT data collected incidentally. Therefore, it was insignificant what time point patients' were in their disease trajectory, rather we just needed to know if the data collection processes were feasible and acceptable to them (Appendix 1, publication 7, section 4, para 1).
Data collection	This aspect of the study method was challenging in terms of ensuring the data collection processes were acceptable at all international sites. I conducted discussions with colleagues at international meetings to better understand the clinical pathway across countries. I needed to be pragmatic to ensure the final study method could be adapted to address cultural diversity across international research centres. For example, providing a choice of methods for participants' to return the COMPACT questionnaire, rather than via mail alone, as the quality of postal systems are variable and pre-paid envelopes are not used in all countries. The study was designed to collect data on only two occasions: (1) Time 1 - to collect COMPACT on paper and (2) Time 2, - to complete COMPACT via the preferred method of data collection (paper or electronic) which was selected at Time 1. In addition, I wanted to gather feedback about the experience of completing the questionnaire from patients, and the experience of following the study method and using ALEA from clinicians. The content of these feedback questionnaires will be informed by the information collected during the process of delivering the study. Initially, I had proposed holding a focus group at each site to gather feedback from the participants, however this was reconsidered after discussion with several of the PI's at an international meeting. I learnt that focus groups were not well-attended or considered an acceptable forum in several cultures, due to a desire for privacy. Although recommendations include 4 potential data collection time points for the future registry (Publication 6), for the purposes of meeting the aims of this feasibility study, data collection on two occasions was considered sufficient and would answer the research question while reducing the burden on the participants' (patients and clinicians).
Data analysis	It will not be necessary to conduct statistical analyses as it will be the *feasibility and acceptability* of collecting data that will inform the future processes for the registry. Data to be collated will include: total number of patients recruited per centre; consent rate; participation rate; loss to follow-up; and percentage response to COMPACT questions. The key findings from the patient and clinician feedback questionnaires will be identified and synthesized to inform the final documents and processes.

3.7.3 Compiling the protocol

I compiled the study protocol using a template informed by: (1) existing protocols developed by the CRPS research team (2) the Health Research Authority template (HRA, 2018b).

3.7.3.1 Documentation included in the protocol

In order to use the PROMs within the COMPACT questionnaire, permissions were obtained from the respective distributors or licence holders (Appendix 1, publication 7, 3.4) (Table 3.15). This took considerable time and diligence, for example, screenshots of the electronic version of the questionnaire had to be approved by some licensors. The formatting of the COMPACT questionnaire necessitated some changes to the layout of some PROM's and these changes had to be conveyed to the licensors and approved.

Translation of some questionnaire outcome measures and study documents would be required prior to delivering the protocol (Appendix 1, publication 7, section 9) (Table 3.15). I subsequently delivered this during the study.

Table 3.15: Documentation included in the protocol

Study documentation	**Permissions**	**Translation required**				
		French (Canada)	**German (Switzerland)**	**Hebrew (Israel)**	**Japanese**	**Portuguese (Brazil)**
COMPACT baseline questionnaire[a,b]	Required for 5 PROMs in several languages	✓	✓	✓	✓	✓
COMPACT follow up questionnaire[a,b]	Required for 5 PROMs in several languages	✓	✓	✓	✓	✓
CRPS severity score	Required	✓	✓	✓	✓	✓
Feasibility study documentation[c]**;** Protocol, consent form, PIS, invitation letter, contact details form, text for EDMS, Time 2 paper completion letter, reminder letter for paper and electronic completion.	Not applicable	✓	✓	✓	✓	✓

[a] See publication 7, table 1 for included PROMs
[b] USA and Australian-specific PROMs inserted into English language COMS where applicable
[c] Study documentation prepared in a UK and generic version

3.7.3.2 Ethics and governance

I was responsible for ensuring the protocol complied with UK ethical and governance requirements and examples of these are provided in Table 3.16.

Table 3.16: Ethical and governance considerations

Ethical and governance considerations	Action and justification
Seeking appropriate sponsorship for the study	I was responsible for liaising with the host NHS Trust R&D department to seek agreement that the Trust would sponsor the study. This was necessary to ensure that the Trust would hold overall responsibility for the management, financing and liability of the study (HRA, 2018a).
Obtaining UK ethical approval for the study	I prepared the UK ethics submission (Appendix 1, publication 7, section 8).
For centres outside the UK, the local principal investigator would seek the relevant ethical approvals	The rationale for this was multi-factorial and included: (1) this was beyond my scope in terms of professional practice (2) I was not familiar with local requirements and processes (3) many applications would be in the local language. I would provide the international researchers with support in terms of information and documentation in order for international approvals to be obtained in a timely manner.
Completion of COMPACT questionnaires by participants would require consideration of their current health status, which may evoke negative feelings	I ensured the study was designed to comply with Good Clinical Practice guidelines, to ensure the research participants' rights, safety, and well-being were protected (NIHR, 2019b). I sought advice from a Clinical Psychologist colleague to ensure this was addressed in the protocol according to best practice (Appendix 1, publication 7, section 8).
Preparation of the data management plan which outlined how the study data would be collected, managed, shared and stored	I was responsible for preparing the data management plan. I sought advice and information from the team designing and hosting the EDMS to ensure I represented the technical aspects accurately, for example, information about where the data servers were situated and procedures for backing up the data (Appendix 1, publication 7, section 7). It was important to ensure that I complied with the new General Data Protection Regulation in terms of ensuring the study documentation provided the participants with information regarding why their data were being collected, how data were to be collected and stored, and for how long (GDPR, 2018).

3.7.4 Funding application

To fund the study described in the protocol, I capitalised on my previous collaboration (publication 6) and prepared a successful funding application to a Swiss insurance organisation. It was my first experience of preparing a budget and timeline for a multi-centre study and, on reflection, it would have been beneficial to follow an existing template in order to attribute costs in more detail (HRA, 2018a). I was also successful in obtaining a smaller grant from Trust Charitable Funds. Subsequently, I have successfully managed the budget to date.

3.7.5 New developments

This protocol paper does not generate new knowledge in the field of CRPS however, the findings will inform the final data collection and management process for the first international CRPS clinical research registry. New developments resulting from Publication 7 are listed in Table 3.17.

I was responsible for identifying and registering the protocol on an appropriate primary clinical trial registry (ISRCTN33817530). Protocol registration is recognised as best practice in order to promote transparency, reduce duplication of research and prevent selective reporting (Keefe *et al*. 2018; Lee *et al*. 2018).

Table 3.17: New developments resulting from Publication 7

New developments	• Identification of the first bespoke ALEA EDMS for CRPS, which will form the future international registry
	• Design of the first international protocol to test the feasibility and acceptability of collecting data for CRPS clinical studies using a core measurement set

3.7.6 The publication

As first author, I selected the publication 'Musculoskeletal Care' (Wiley) for the submission as I identified that it had previously published protocols and would reach a relevant audience. I prepared the first draft of the manuscript, and revised this in response to comments from co-authors. For the first time, my submitted manuscript was accepted without revisions.

Publication 7 gave me opportunities to communicate with colleagues from different cultures and health systems. Having presented at national and international meetings, I am a confident public speaker and am well equipped to promote the importance of the COMPACT initiative to a wider audience. Undertaking this work inspired me to develop my leadership skills further, attaining a competitive place on the one year, NIHR Advanced Leadership Programme in 2017. This was directed at those delivering NHS research and comprised a more specific and in-depth programme than my previous Frontline course.

Publication 7 demonstrated that I was able to effectively set-up a multi-centre study and, as a result, I was invited to lead a work package within a Versus Arthritis-funded research programme[3] I was a co-applicant on this grant and responsible for leading the clinical trial which completes the staged programme.

[3]Versus Arthritis https://www.versusarthritis.org/media/2002/medical-technology-proof-call-document.pdf

3.7.7 RDF domains achieved

All twelve RDF sub-domains were achieved whilst designing the research protocol presented in Publication 7 (Table 3.18).

Table 3.18: RDF sub-domains achieved in Publication 7

RDF Sub-domain achieved	Descriptor
A1: Knowledge base	Subject knowledge
	Research methods: theoretical knowledge
	Research methods: practical application
	Information seeking
	Information literacy and management
	Languages*
	Academic literacy and numeracy
A2: Cognitive abilities	Critical thinking
	Evaluating
	Problem solving
A3: Creativity	Inquiring mind
	Intellectual insight
	Innovation
B1: Personal qualities	Responsibility
	Self-reflection
	Enthusiasm

	Perseverance
	Integrity
	Self-confidence
B2: Self-management	Responsiveness to change
	Commitment to research
	Preparation and prioritisation
	Time management
	Work-life balance
B3: Professional and career development	Networking
	Reputation and esteem
C1: Professional conduct	Ethics, principles and sustainability
	Health and safety
	Legal requirements
	IPR and copyright
	Respect and confidentiality
	Attribution and co-author
	Appropriate practice
C2: Research management	Project planning and delivery
	Research strategy
	Risk management
C3: Finance, funding and resources	Income and funding generation
	Financial management
	Infrastructure and resources
D1: Working with others:	Team working
	Influence and leadership
	Collegiality
	Supervision
	Mentoring
	People management
	Equality and diversity
	Collaboration
D2: Communication and dissemination	Communication methods
	Publication
	Communication media
D3: Engagement and impact	Public engagement
	Global citizenship

***** Descriptors in bold are newly acquired as a result of this publication

3.8 Publication 8

Publication	Journal and Impact Factor	My contribution
Grieve, S., Llewellyn, A., Jones, L., Manns, S., Glanville, V., McCabe, C. (2019b) **Complex Regional Pain Syndrome: An international survey of clinical practice.**	**European Journal of Pain** 23(10), pp.1890-1903 IF: 2.991	**Study:** • Contributed to design of study and survey. • Designed and wrote the protocol • Supervised the building of the survey using Qualtrics • Contributed to pilot testing. • Undertook qualitative data analysis and contributed to quantitative data analysis. • Presented posters at national and international conferences **Paper:** • First author. • Wrote first draft and revised subsequent drafts. • Submitted paper

3.8.0 Background

Publication 8 arose from my clinical experience within the CRPS service, and that of my clinical colleagues, which indicated that CRPS clinical practice varied widely, at a local, national and international level. This is despite a number of published country-specific and generic treatment guidelines, which promote best practice in CRPS treatment and management (Goebel, Barker, Turner-Stokes *et al.* 2018; Perez *et al.* 2014; Harden *et al*. 2013). Recently, a European Task Force was convened to find ways to address this anecdotal variation in care, but there was no clear understanding of what existing care actually comprises (Goebel *et al*. 2019).

Using networks established via the PROactive collaboration (Chapter 1, p.16) to establish a new team of appropriately skilled researchers, an international e-survey was conducted to gain insight into routine CRPS clinical practice. This sought to identify the barriers and facilitators health professionals internationally encountered in their CRPS clinical practice, and to explore whether these were specific to their location or had a wider relevance. The importance of this work was supported by the CRPS European Standards Task Force, who had suggested that a survey of current practice should be conducted to establish what constitutes

regular clinical practice relative to the newly defined standards of care (Goebel *et al*. 2019).

My past experience as a Principal Investigator (publication 4) enabled me to take a leading role in this research. It was undertaken concurrently with the COMPACT work (Publication 6 & 7) as my full-time salary has never been funded by a single study.

3.8.1. Methodology

This was my first experience of designing and conducting a survey, and required me to become proficient with a new methodology.

I selected a web-based survey design (e-survey) as it provided a quick and inexpensive way of collecting data from a large group of people across an international population (Braun and Clarke, 2013). A recent meta-analysis found online surveys via email yield lower response rates than other survey modes as they are often overlooked (Daikeler, Bošnjak and Lozar, 2019) however, a paper-based survey was considered, but rejected, due to cost and administrative burden (Parsons, 2007). I anticipated that those with an interest in CRPS were likely to respond as this was an under-researched topic and would provide much-needed data.

I used a convenience sampling strategy to optimise response rates (Gerrish & Lathlean, 2015) although this has also been argued to result in respondents not being representative of the population under investigation (Coughlan, Cronin and Ryan, 2009). In the light of this potential limitation, I sought to optimise responses from the target population by recruiting participants internationally via targeted advertisements on web pages of professional bodies and CRPS special interest groups (Saleh and Bista, 2017). More personalised approaches, cash incentives and reminders have all been shown to improve survey response rates (Smith, Bélisle-Pipon and Resnik, 2019; Saleh and Bista, 2017) however, we wished to maintain anonymity of respondents to encourage candid responses (Parsons, 2007) and therefore chose not to issue personal invitations to participate.

I designed and wrote the protocol for the survey, selecting a mixed methods approach and using a parallel design where both qualitative and quantitative data had equal value, an approach which is widely advocated in health and social research (Yardley and Bishop, 2015; Tariq and Woodman, 2013). A cross-

sectional, descriptive approach was appropriate for the observational nature of enquiry which intended to elucidate the characteristics and behaviour of respondents (Bowling, 2014).

3.8.2. Survey content

The survey content was developed in collaboration with the CRPS research lead and UWE colleagues (Appendix 1, publication 8, 2.1). Questions were informed by the research team members' experience of delivering a national CRPS service and best practice in the management of CRPS (Goebel, Barker and Turner-Stokes *et al.* 2012). On reflection, input from international colleagues would have provided a wider perspective and ensured that questions had a broader relevance, for example, taking into account country-specific variations in health care systems in the response options available.

Several survey response options were considered including: provision of a drop down menu, free text and polar responses (Appendix 1, publication 8, table 1). Options selected aimed to reduce participation burden, for example, a drop down menu is quicker to complete and provides a standardised response for analysis (Parsons, 2007). Conditional questions, based on a previous response, also reduced the burden for respondents as they were not asked irrelevant follow-up questions (Swanson *et al.* 2014).To reduce the likelihood of missing data, the final version incorporated forced responses which had to be completed in order to move to the next question. It has been argued that this risks respondent's withdrawing from the survey if their preferred response is not listed (Parsons, 2007), therefore I made careful effort to anticipate all potential responses and provide options accordingly.

Regrettably, resources were not available to translate the e-survey into multiple languages and therefore, I made it as accessible as possible to those where English was their second language. To optimise readability by this population, I piloted the survey using an existing network of colleagues whose first language was not English, (Appendix 1, publication 8, 2.1). It was possible, that the free text option may have deterred those non-fluent in English (Appendix 1, publication 8, 3.1.1), and the results did demonstrate higher returns from countries where English is the first language. However, a breadth of countries were represented

across many continents indicating that, providing the survey in English only did not prevent responses from these areas.

3.8.3 Data analysis

This was my first experience of using online survey software. An advantage of using an e-platform was that response data were able to be exported directly to a spreadsheet in readiness for analysis (Polit and Beck, 2017). To maintain the integrity of the data, each data set was analysed according to the relevant methodology (inductive thematic analysis and descriptive statistics), and then the findings from the qualitative and quantitative data were compared and contrasted (Tariq and Woodman, 2013). Details of these methodologies are given below.

A quantitative methodology was used to analyse the majority of the survey data. I used descriptive statistics to describe and summarise these data, for example frequency counts for the categorical variables. Inferential statistical analysis was not conducted as this was not an experimental study; I was not testing a hypothesis or looking for a relationship among variables or difference between the groups (Pallant, 2016; Parahoo, 2014).

Inductive thematic analysis was applied to free text response data in order to search for any aspects of relevance to the research question. (Appendix 1, publication 8, 2.4.2). My previous experience of using the NVIVO data management software (publication 4) ensured the coding process was efficient. As with publication 4, I used a tactile approach and used paper to map the themes within the dataset. I analysed the data with two other researchers from different professional backgrounds and epistemologies. Although the value of having more than a single coder is contested within qualitative research (Braun and Clark, 2013), I found that a strength of this analysis was drawing on our different perspectives which maximised the contribution of differing knowledge, interests and approach when interpreting the data (Green and Thorogood, 2011). Once coding was completed and initial themes generated, my role was to generate the supra-themes across the data set and agree these with my co-researchers (Appendix 1, publication 8, 2.4.2).

3.8.4 Collaboration

Publication 8 evidences my development as a researcher as I contributed to every stage of the study, from inception to dissemination. This study required me to work

with colleagues across organisational boundaries and taught me the importance of clearly defining roles and agreeing a work schedule. During this time, I also mentored a Versus Arthritis intern which gave me the opportunity to develop research supervisory skills by inviting her to contribute to the quantitative data analysis.

3.8.5 New knowledge

This was the first international survey reporting data from such a diverse range of health professionals, academics and researchers, with the aim to better understand the delivery of CRPS care globally (Table 3.19).

Despite the Budapest CRPS diagnostic criteria having being published almost a decade earlier, the e-survey highlighted a range of other criteria being utilised by the respondents (Appendix 1, publication 8, 3.1.1, para 4). This highlights the need for more work to raise awareness amongst clinicians of the Budapest criteria, so as to promote early diagnosis and intervention (Harden *et al*. 2010). Repeating this aspect of the survey in a European population should be considered at a later date to measure the impact of the recently published European standards, which insists that the Budapest diagnostic criteria be used (Goebel *et al.* 2019).

The qualitative data in this study presented new knowledge in relation to highlighting macro-regional variations in clinical practice. By better understanding the delivery of care, this will provide an opportunity to target health provision more effectively. This may inform future service design, and initiatives to promote the implementation of clinical guidelines and best practice.

Table 3.19: New knowledge generated from Publication 8

New knowledge generated	• It was identified that health professionals have a lack of awareness of the Budapest diagnostic criteria
	• It was identified that health professionals have difficulty diagnosing people with CRPS, even after having worked with these populations for a number of years
	• It was identified that there are macro-regional variations in clinical practice

3.8.6 The publication

As first author, I wrote the first draft of the paper and refined it in response to comments by my co-authors. I submitted the manuscript to the 'European Journal of Pain' (Wiley) as it had recently published the CRPS European Standards (Goebel *et al*. 2019) and had an impact factor of 3.188. This implied a wide audience and would maximise international readership. Responding to reviewers' comments, in the second iteration I mapped our data onto a framework which categorised the barriers to guideline implementation, thereby identifying variations in the reported macro-regional barriers (Fischer et al. 2016).

Findings were disseminated widely as they were of interest to national and international clinicians in the field of CRPS. I presented a poster at the British Pain Society Annual Scientific Meeting (Grieve et al. 2017a) and at the 17th World Congress on Pain in Boston, USA (Grieve *et al*. 2018). As part of my DPhil registration, I presented this work at the UWE Centre for Health and Applied Sciences Showcase Conference and was awarded the prize for best student poster (Grieve *et al*. 2019c).

3.8.7 RDF domains achieved

Eleven RDF sub-domains were achieved whilst undertaking the research presented in Publication 8 (Table 3.20). No new descriptors were acquired however, I was able to consolidate those already achieved.

Table 3.20: RDF sub-domains achieved in Publication 8

RDF Sub-domain achieved	Descriptor
A1: Knowledge base	Subject knowledge
	Information seeking
	Research methods: theoretical knowledge
	Research methods: practical application
	Information literacy and management
	Academic literacy and numeracy
A2: Cognitive abilities	Analysing
	Synthesising
	Critical thinking
	Evaluating
A3: Creativity	Inquiring mind
	Intellectual insight
	Argument construction

B1: Personal qualities	Responsibility
	Self-reflection
	Enthusiasm
	Perseverance
	Integrity
	Self-confidence
B2: Self-management	Preparation and prioritisation
	Responsiveness to change
	Commitment to research
	Time management
	Work-life balance
B3: Professional and career development	Networking
	Reputation and esteem
C1: Professional conduct	Ethics, principles and sustainability
	Legal requirements
	IPR and copyright
	Respect and confidentiality
	Attribution and co-author
	Health and safety
	Appropriate practice
C2: Research management	Project planning and delivery
	Research strategy
	Risk management
D1: Working with others	Collegiality
	Influence and leadership
	Team working
	Collaboration
	Supervision
	Mentoring
	People management
	Equality and diversity
D2: Communication and dissemination	Publication
	Communication media
	Communication methods
D3: Engagement and impact	Teaching
	Global citizenship

3.9 Summary of Chapter 3

Chapter Three has presented the eight publications which comprise this thesis. Each has been accompanied by a critical commentary presenting my individual contribution to the original research, my personal and professional development as a researcher in the context of the publication, and new knowledge generated. I have demonstrated how all eight publications culminate in my achievement of all 12 sub-domains within the RDF (Appendix 4) (Vitae, 2010). This will be discussed further in Chapter 4.

Chapter 4: Discussion

4.0 Overview of Chapter 4

The previous chapter presented eight publications which comprise this thesis. My contribution to new knowledge, through original research was highlighted. I have evidenced how I have achieved all 12 sub-domains within the RDF in order to demonstrate my academic and clinical competence as an independent researcher (Appendix 4) (Vitae, 2010).

Chapter Four will reflect on the different research philosophies used in the publications presented. The key research findings presented in this thesis will be discussed and I will demonstrate how these findings have contributed to a greater understanding of the mechanisms and management of chronic pain, and specifically CRPS. The research was undertaken with the aim to improve health outcomes for people experiencing chronic pain and I will describe the clinical impact of my research. Areas for future research will be identified. Reflections on undertaking this thesis will be shared and I will describe how I have developed as an independent nurse researcher and a research nurse leader.

4.1 Reflection on the research philosophies underpinning the thesis

A research philosophy constitutes a set of assumptions that provide a framework, or paradigm, which underpins the researcher's personal beliefs in relation to truth, reality and knowledge (Allsop, 2019; Ryan, 2018). These assumptions comprise two concepts; (1) ontological assumptions are those made about the nature of reality and the relationship between the world and our understanding of it (Corry, Porter and McKenna, 2019; Braun and Clarke 2013); (2) epistemological assumptions are those made about the nature of knowledge and the steps researchers' take to gain knowledge of the area of study (Braun and Clarke, 2013).

Initially, as a novice researcher, the inconsistencies with which research philosophies were described within text books resulted in a lack of clarity of how to unpick my own theoretical perspective (Corry, Porter and McKenna, 2019). However, the process of undertaking Masters' degree level modules ensured a more in-depth understanding and I recognised that the approach or methodology I selected, the methods I used, and my epistemological and ontological assumptions, were intertwined and co-dependent.

My publications are underpinned by a range of paradigms encompassing positivism or interpretivism. Publication 3 adopted a positivist approach, utilising a quantitative methodology, where there is a confirmable observation of empirical events using the scientific method. The aim of a positivist approach is to uncover an objective truth by setting aside the researcher's preconceptions (Corry, Porter and McKenna, 2019; McEvoy and Richards, 2006). This approach is most widely attributed to the randomised controlled trial, however it also includes structured questionnaires (Publication 7) and systematic reviews (Publication 5). The positivist approach aligned closely with my experience as a nurse, as I was familiar with the use of measurement and observation within patient care. The advantage of positivism is that it has the ability to generate generalisable, replicable findings which adds to the rigour, validity and reliability of the research study (Allsop, 2019). However, I was mindful that positivism comprises measures constructed by the researcher and does not necessarily represent those factors that are important to the patient (Allsop, 2019). Increasingly, over the course of my studies, I found I was able to justify the decision to adopt or reject a particular philosophical approach (Ryan, 2018).

Publication 2, 4 and 8 adopted an interpretivist approach, applying a qualitative methodology, which places a much greater emphasis upon the way in which the world is socially constructed and understood (Parahoo, 2014). In contrast to positivism, interpretivism maintains that truth and knowledge are subjective (Ryan, 2018). Publications 2, 4 and 8 incorporated an inductive, phenomenological approach which focused on the interpretation of people’s experiences which allowed the researcher to find meaning from multiple perspectives (Weaver and Olson, 2006). Initially, I struggled to make sense of how my own values and beliefs would inform my research methods and the interpretation of the results (Ryan, 2018). However, I came to appreciate how the interpretivist paradigm aligned with the nursing model of patient-centred care and the value of exploring the meaning patients place on their experience of living with chronic pain.

4.2 Scientific contribution and impact on clinical care

Of the eight publications included in this thesis, six presented primary research (publications 2-6 & 8). The key findings of these six papers are presented in Table 4.1, p.88. The publications within section 4.2 are discussed in relation to topic heading rather than in numerical order.

Table 4.1 : Key findings presented in this thesis

Publication	New knowledge generated
2	A novel method of communicating changes in body perception was developed.
	A novel method of representing changes in body perception using digital media was developed.
3	A new hypothesis that pain lowers the threshold for the detection of sensorimotor conflicts, a phenomenon that could contribute to the maintenance of pain in clinical populations.
	Sensory disturbances were found to be strongly related to the intensity of pain, regardless of the pathology.
	The presence of pain did not make people more prone to feelings of peculiarity and the perception of having an extra limb during sensorimotor conflict
	Two subgroups of conflict- induced sensory disturbances were identified. This suggested that sensory disturbances are potentially related to two different processes and should be considered separately.
4	There was a gap between what information was needed by a person with CRPS and what information they were able to access.
	There was a reported lack of appropriate and timely information available for those with CRPS.
5	Patient or health professional-reported questionnaire outcome measures, used in CRPS clinical trials between 2000-2014, were identified.
	Patient or health professional-reported questionnaire outcome measures, which had been developed specifically for use in CRPS populations, were identified.
	A shift towards using health outcomes related to daily functioning in the field of CRPS since 1998 was identified.
6	The first questionnaire COMS for CRPS clinical studies was agreed by an iterative process of consensus.
	A novel method of collecting standardised CRPS outcome data was developed.
	The first published recommendations for the collection of CRPS outcome data in international research practice.
8	It was identified that health professionals have a lack of awareness of the Budapest diagnostic criteria
	It was identified that health professionals have difficulty diagnosing people with CRPS, even after having worked with these populations for a number of years.
	It was identified that there are macro-regional variations in CRPS clinical practice.

4.2.1 The mechanisms of chronic pain

Publication 3 contributed towards improving our understanding of chronic pain mechanisms and added to the body of knowledge and current theories discussed in Chapter 2 (2.2.2, p.22). A new hypothesis was proposed: that *pre-existing* chronic pain lowers the threshold for the *detection* of sensorimotor conflicts, and that the presence of a sensorimotor conflict may contribute to pain *maintenance* in patient populations. This was in contrast to pre-existing theory which had suggested the *presence* of sensorimotor incongruence may *contribute to* the *generation* of pain, and other sensory disturbances rather than *maintaining* pre-existing pain in chronic pain pathologies (Don *et al.* 2016*;* Harris,1999). Publication 3 demonstrated that, *in the presence of pain*, sensorimotor conflict does also induce people to report *new* conflict- induced sensory disturbances. The new sensory disturbances could be categorised into two distinct sub-groups, suggesting two different processes of cortical activation, and supporting the results of previous electroencephalogram studies (Katayama *et al.* 2016; Nishigami *et al*. 2014).

Evidence had suggested, that in the presence of pain, people are more likely to report changes in sensory perception in response to sensorimotor conflict than people who are pain-free (Daenen *et al*. 2012a; Daenen *et al*. 2012b). Publication 3 extended this work by demonstrating that pain intensity is a strong predictor for sensory disturbances to be generated by a sensorimotor conflict, regardless of the pain condition. One limitation of Publication 3 was the pre-defined order of the experimental conditions; a randomised approach would have reduced bias (Bowling, 2014).

Building directly on the findings from Publication 3, my co-authors have proposed a further hypothesis to explain where in the motor control system the sensorimotor conflict lies (Brun, McCabe and Mercier, 2020). This extends the model of the motor control system proposed by Frith *et al.* (2000) (Fig. 4.1, p.90). Brun, McCabe and Mercier (2020) demonstrated that, for people with fibromyalgia, sensorimotor conflict does not arise from the motor performance aspect of the motor control system, but in the sensory aspect, specifically between what is actual sensory feedback versus what is predicted sensory feedback from the motor command (Fig. 4.2, p.90: from Brun, McCabe and Mercier, 2020). Future work should explore these findings in other pain populations.

Fig 4.1: The basic components of a motor control system based upon engineering principles. In Frith *et al.* (2000). Republished with permission of The Royal Society (UK), from 'Abnormalities in the awareness and control of action', Frith, Blakemore and Wolpert, (2000) 355, p.1773; permission conveyed through Copyright Clearance Center, Inc.

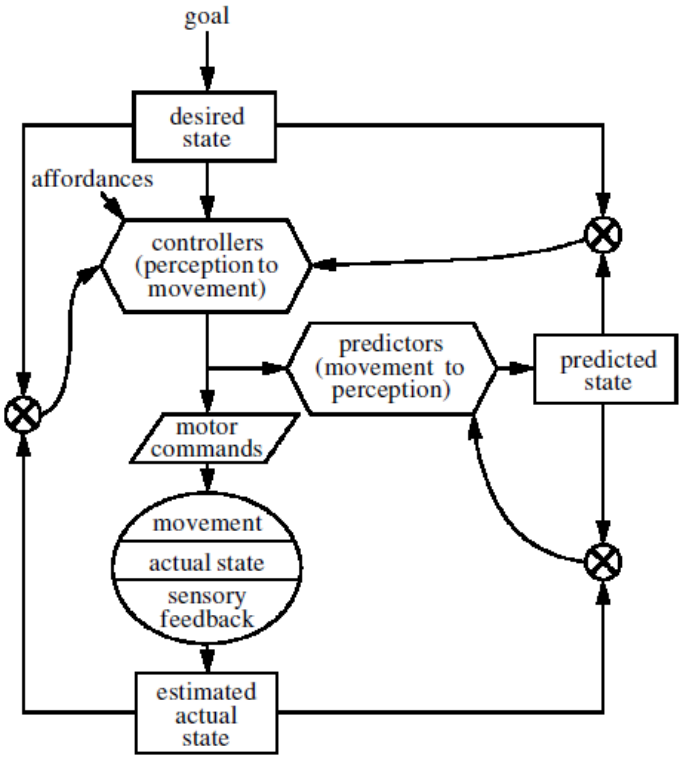
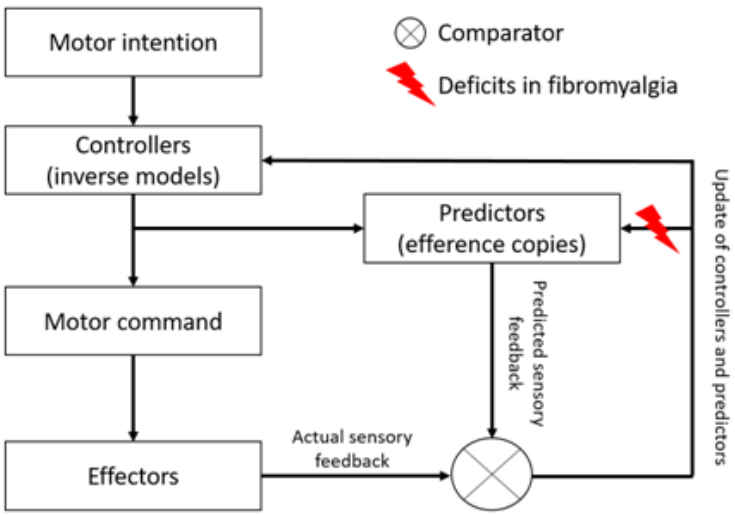


Fig 4.2: Internal models of motor control. Errors issued from the comparison between the actual and the predicted sensory feedback are used to update the controllers (the control of action) and the predictors (the perception of action). Neuroscience (in press) Brun, McCabe and Mercier (2020). The contribution of motor commands to the perturbations induced by sensorimotor conflicts in fibromyalgia, Copyright Elsevier (2020). Permission to reprint granted.



4.2.2 Sensory disturbances in chronic pain and CRPS

Publication 2 (thesis, p.36) presented a novel method of communicating and representing changes in body perception in CRPS, using digital media. However, when introduced in CRPS clinical practice, health professionals reported the BPT to be time-consuming to implement (Publication 2, 3.2.4). Application of the BPT was subsequently investigated in a stroke research setting (Stott *et al*. 2019). However, similar limitations were reported by participants, in terms of the time required to implement the BPT (Stott, 2019). This indicates that, without further funding to modify the software, it is unlikely to be implemented in a time-pressured clinical environment. The limitations associated with using the BPT in a clinical setting suggest that future research should focus on developing technology for independent patient use. This would mitigate the need for health professionals to administer the tool and would promote patient self-management (Demain *et al.* 2013; Oliveira *et al.* 2012). This would also provide scope for the technology to be used in a home-setting.

The research presented in Publication 2 was conducted seven years ago and there has been progress in use of digital media to assess BPD. For example, a recent study used an avatar to replicate a full-body image, in order to assess body perception on movement (Roosink *et al*. 2015). However, there is evidence that researchers continue to search for the gold standard in evaluating and measuring body perception disturbance in chronic pain (Tsay *et al.* 2015). Tsay *et al*. (2015) included Publication 2 in a review of the literature that involved the subjective appraisal of body representation in patients with chronic pain, and acknowledged the value of using tools to gain insight into the patients' experience. The tool developed in Publication 2 was presented as the only example of a digital application, indicating a need for further work in this area.

Researchers continue to investigate the mechanisms which contribute to BPD (Brun *et al*. 2019; Don *et al.* 2017). Evidence indicates that the process within the somatosensory cortex, which generates an individual's perception of their body *image*, is independent of the process which generates their awareness of their body in space, the body *schema* (Schwoebel and Coslett, 2005; Schwoebel *et al.* 2001; Paillard, 1999). This has implications for rehabilitation, as it suggests therapies should be targeted to improve either the individuals' body schema or body image. A recent study demonstrated a significant reduction in body

perception disturbance after a two week multi-disciplinary rehabilitation programme for CRPS (Lewis *et al.* 2019). A significant correlation was found between a change in BPD and reduction in pain intensity, and it was suggested that if rehabilitation is targeted to improve BPD, pain may also improve (Lewis *et al.* 2019). It was not evident which components of the rehabilitation targeted body schema or body image however, future research could investigate this further. Recording changes in BPD before and after rehabilitation may provide a useful way of measuring progress in rehabilitation (Lewis *et al.* 2019).

4.2.3 Management of CRPS

4.2.3.1 The information needs of people with CRPS

Publication 4 provided new insights into the information needs of people with CRPS and identified a gap between the information people with CRPS reported they needed, and the information they were able to access (Table 4.1). The quality of information sources used by patients has been shown to influence the quality of their treatment decision-making (Packham *et al*. 2017; Garneau *et al.* 2011; O'Connor, Mulley and Wennberg, 2003). This aligns with the research presented in Publication 4 as participants reported that a lack of information led to poor engagement with rehabilitation. The insights gained in Publication 4 could be used to tailor patient information to address specific CRPS information needs which may contribute to improving health outcomes.

In response to the participants' desire for reputable resources, I added health professional-recommended literature and websites providing information about CRPS, to a CRPS-specific website which provided open access to the public (https://www.crpsnetworkuk.org/). Since Publication 4, the Bath CRPS service, has designed and implemented a website to provide information and support to patients' undertaking the national, specialist in-patient CRPS programme (unpublished). Future research should evaluate the impact of this educational resource on self-management of CRPS.

Although the research presented in Publication 4 was conducted eight years ago, few research studies have further explored this important aspect of CRPS clinical care. Louw *et al. (*2018) describe how Publication 4 informed the development of their survey questions when they investigated the beliefs and experiences of people with CRPS. This survey indicated there has been little progress since

Publication 4, as patients continued to report they had a lack of understanding of CRPS, its management and potential outcomes (Louw *et al.* 2018).

Two recent editorials have discussed Publication 4 in the context of qualitative research in CRPS (Breivik and Butler, 2017; Butler, 2015). Although it is recognised that editorials are low in the hierarchy of evidence (Ingham-Broomfield, 2016), the patient-orientated focus of Publication 4 is commended (Butler, 2015).

Both the European Standards for the diagnosis and management of CRPS, and the UK guidelines for the management of CRPS in adults, recommend that health professionals should provide patients with information to educate them about CRPS (Goebel *et al*. 2019; Goebel, Barker and Turner-Stokes *et al*. 2018). However, despite one example within the guidelines, there is little evidence of what this should look like in terms of content. This paucity of data informed a recent student research study that I supervised, which aimed to assess the quality of online educational resources for people with CRPS (Fry *et al.* 2019). Relevant online materials were examined from three popular internet search engines and was found to be inadequate in terms of: quality, reliability, and failure to meet the recommended standards of readability for health information (Fry *et al.* 2019). Future work is required to evaluate a broader range of educational resources, mapping these to research-identified patient needs and current UK guidelines (Fry *et al.* 2019). It would be of interest to explore whether the quality of online educational resources is similar across other chronic pain populations (Devan *et* al. 2019; des Bordes *et al.* 2018). Future research should assess the impact of recently published CRPS European standard 8 (Goebel *et al*. 2019) and consider whether this results in resources being directed into this aspect of clinical care.

Encouragingly, there is evidence that health professionals are recognising the importance of addressing patients' information needs. A recent international survey of current practice in CRPS rehabilitation amongst clinicians, reported that education, along with physical exercise, was the most frequently used rehabilitation approach however no detail was provided as to what the education comprised (Miller, *et al.* 2017). In addition, the European Pain Federation CRPS task force is currently undertaking a Delphi survey of healthcare professionals and patients, to explore the education needs of people with CRPS and to identify recommended resources (unpublished). Once published, this will be a useful

article to sign-post patients and health professionals to current resources, however future work will be needed to maintain its contemporaneous nature.

4.2.3.2 Contributing to the understanding of international CRPS clinical practice

Publication 8 was the first survey to be undertaken in a diverse population of health professionals, with the aim to better understand the current provision of CRPS care internationally. One of the key findings reported was a lack of health professionals' awareness of the recommended Budapest CRPS diagnostic criteria, despite being published almost a decade earlier (Harden *et al*. 2010).

The European Standards for the diagnosis and management of CRPS have stated that the Budapest criteria must be used as a diagnostic tool as they provide acceptable sensitivity and specificity (Goebel *et al.* 2019). The Standards were not published when the Publication 8 e-survey was conducted, and so it would be relevant for future research to repeat this aspect of the survey to assess the Standards' impact on clinical practice. Publication 8 may provide a framework on which to compare future findings.

Goebel *et al.* (2019) recommend raising awareness of the Budapest criteria via improved training and resources for health professionals and patients. The recently updated UK CRPS guidelines are a freely available resource (https://www.rcplondon.ac.uk/guidelines-policy/complex-regional-pain-syndrome-adults) (Goebel, Barker and Turner-Stokes *et al*. 2018) and future work could comprise a marketing campaign prior to repeating relevant aspects of the Publication 8 e-survey.

Publication 8 identified macro-regional variations in CRPS clinical practice. These regional variations are recognised by the European Task Force who highlighted the need for realistic, country-specific goals (Goebel *et al*. 2019). A diagnostic standard quality framework has been developed for CRPS which would enable stakeholders to benchmark current practice and identify where to target future resources (Goebel *et al.* 2019). Future research is required to establish the uptake and impact of these recommendations.

4.2.4 Contributing to the development of an international CRPS clinical research registry

Publications 5, 6 & 7 evidence my ability to conceptualise, design and implement a project for the generation of new knowledge. The research was conducted over a six-year period and exemplifies how I applied my newly acquired knowledge and skills to drive the research agenda towards the development of a COMS for CRPS research.

The three publications contributed to an ongoing, iterative programme of research which will inform the development of a long-term, international CRPS clinical research registry. High quality evidence, from large clinical studies, is required to evaluate the effectiveness of treatments for CRPS (O'Connell *et al.* 2013). For the first time, the registry will provide access to a large data set of standardised, CRPS-specific, outcomes for interrogation. In the long-term, this may improve health outcomes for the CRPS population worldwide as this will enable researchers to better understand the potential phenotypes of CRPS and prognostic indicators, which may impact clinical care through the development of targeted therapeutic approaches.

The impact of this work in the field of chronic pain and CRPS is indicated by the number of citations in peer-reviewed literature. To date, publication 5 has been cited 13 times and publication 6 has been cited 19 times (https://scholar.google.com/citations). The publications that reference this work include a narrative review summarising recent developments relating to PROMs in chronic pain (Pogatzki-Zahn, Schnabel and Kaiser, 2019). Although a review is considered low level evidence, it is noteworthy that Publication 6 is presented as an example of a COMS in a chronic pain condition alongside the initiatives; OMERACT(Boers *et al*. 2014) and IMMPACT (Turk *et al*. 2003). The review supports evidence which emphasises the important role consensus-based COMS play in order to facilitate comparison of research findings and reduce reporting bias (Pogatzki-Zahn, Schnabel and Kaiser, 2019; Chiarotto *et al*. 2017).

Future research will comprise the delivery of the protocol presented in Publication 7. I am currently co-leading this multi-centre, international, feasibility study across seven international research centres, thereby increasing the external validity of this research. The results will be discussed at an international meeting in 2021,

and the final processes for the international registry agreed via a consensus process. Following this, I will prepare a paper reporting the findings and will be submit this for publication in an appropriate, international peer-reviewed journal. An important priority for future work, is to raise international awareness of the COMPACT COMS and the clinical research registry amongst potential users, for example researchers and clinicians.

Going forward, I will co-lead the implementation of the international registry including; the design of the registry study protocol, design of the associated study documentation, obtaining UK ethical approvals and international dissemination. Recent research has investigated the implementation of COMS in the field of chronic pain and there is evidence that, although many researchers are familiar with COMS, they are not widely used (Dosenovic *et al.* 2019). This is reflected in the gap between research evidence and translation into clinical practice (Grimshaw *et al*. 2012; Lang, Wyer and Haynes, 2007). Crucially, this may lead to patients not benefiting from advances in care and could also be less cost effective for the health provider (Grimshaw *et al.* 2012). Informed by recent engagement activities from the OMERACT initiative (Tunis *et al.* 2017), future research should identify strategies to promote the uptake of the COMPACT COMS and utilisation of the future registry.

4.3 An independent nurse researcher and research nurse leader

The work presented in this thesis demonstrates how I have acquired the knowledge, intellectual abilities and skills to become an independent nurse researcher and research nurse leader. I have demonstrated that I have achieved the UWE doctoral descriptors (appendix 2). Throughout this thesis, the RDF (Vitae, 2010) provided a thread of connectivity which enabled me to evidence and evaluate my professional and personal development using critical self-assessment and self-reflection (Davies and Rolfe, 2009). This process heightened my awareness of areas of strength and identified outstanding development needs. I have addressed the latter via UWE post-graduate training opportunities for example, 'evaluating the impact of public engagement'.

The breadth of peer-reviewed research presented has evidenced my proficiency in applying different research methodologies across a range of topics in the field of chronic pain and CRPS. For each publication, I have highlighted the originality of

my research. I have exponentially developed a critical judgment of issues and ideas in the field of chronic pain over the seven years spanning the presented publications. This is demonstrated by my increasing contribution to the research design and my ability to adapt this in response to emergent issues (publication 6 & 7).

Undertaking this research provided me with the opportunity to develop collegiate and international collaborations which I will build on going forward. This has included working collaboratively with patients as research partners, and without whom the research would have been diminished. Insights gained from patients continue to inform my research interests and keep the lived experience of chronic pain at its heart. The opportunity to self-evaluate and critically reflect on my research practice has identified areas of research priority and where the greatest impact on patient care could be achieved. For example, for the first time, a large consistent data set will facilitate the comparison of data to answer specific research questions to advance the treatment of CRPS (Publication 7). This will lead to an exploration of how clinical practice impacts health outcomes and, ultimately, the aim is to achieve targeted treatments.

As a registered nurse, I maintain a patient-centred perspective to be able to develop and lead clinically relevant research. A key driver is to be able to demonstrate the clinical impact of my research on patient care. My clinical research role has ensured that my research interests are closely linked to clinical priorities and I am in a key position to influence the adoption of research findings into clinical practice.

Despite a drive to increase the number of clinical academic roles in nursing and midwifery, there is evidence of poor progression towards doctoral studies (Trusson, Rowley and Bramley, 2019; Carrick-Sen *et al.* 2016). Emphasis is placed on the traditional, prospective doctorate (Smith, 2015; NIHR, 2020b). This thesis has demonstrated the value of experiential learning around the practical conduct of clinical research and the theoretical knowledge that underpins research practice. The publications presented in this thesis have advanced research in the nursing profession and have been motivated by a desire to improve outcomes for patients in my field.

The process of compiling my thesis, and evaluating my professional development against the RDF sub-domains (Vitae, 2010), validated my abilities as a leader, particularly in relation to the COMPACT study. This increased my confidence and was instrumental in my application to the NIHR 70@70 programme. My appointment as a NIHR 70@70 Senior Research Nurse Leader has informed the final year of my doctoral studies. This role has provided me with an opportunity to drive the research agenda within my organisation and regional area, for example introducing research measures into my Trust's ward accreditation programme. As an independent clinical academic researcher, I will be able to make a significant contribution to the effective delivery of high quality, chronic pain research within the NHS.

4.4 Reflections on undertaking the thesis

It has been a privilege to validate and reflect on what I have achieved through the process of undertaking a DPhil by Publication. Moreover, this was achieved without the need to sacrifice my research role within the NHS Trust in order to pursue a traditional PhD route. Importantly, this has enabled me to remain at the centre of patient care.

At the beginning of my doctoral journey, I had difficulty in formulating how a DPhil by publication would look. Published resources (Davies and Rolfe, 2007; Smith 2015), the support of my DPhil supervisors, and my fellow DPhil students at UWE, enabled me to navigate this effectively. I had to adopt a new style of ‘thesis’ writing which was challenging when used to writing ‘journal’-style.

I consider myself a pragmatic researcher, pursuing opportunities where they present, whilst still maintaining a focus of improving health outcomes in the field of complex regional pain syndrome to inform chronic pain practice. This has enabled me to gain a critical understanding of the current state of knowledge in a broad range of topics and my thesis has presented a breadth of research within the field of chronic pain. However, it was a challenge to address each topic in sufficient depth within the prescribed word count. To do this, I have included less detail than I may have wished. Conversely, the breadth of topics demonstrates how I have developed a range of expertise which I can apply to my future research interests.

Writing the DPhil over 18 months has required commitment, motivation and exceptional time management. I have concurrently worked full time which included

leading an international study, co-ordinating a site move for the research team and starting a new role as a NIHR 70@70 senior research nurse leader. I was able to manage multiple conflicting priorities. This has been facilitated through the greater resilience I have developed through the implementation of strategies from my leadership training.

Undertaking a DPhil has validated my skills as an independent researcher and given me the confidence to move forward in my career as a nurse researcher to improve health outcomes for people with chronic pain. I have come through this process with a deeper knowledge of my field and I am ready to meet my next challenges with enthusiasm.

4.5 Conclusion

Throughout this thesis I have demonstrated a critical understanding of the current literature and research methods in the field of CRPS and chronic pain practice. The presented publications have evidenced my contribution to the creation and interpretation of new knowledge in this field. I have made recommendations for future research and clinical practice which will drive forward the research agenda by providing a focus for further investigation. I have demonstrated my academic and clinical competence as an independent researcher though my achievement of the 12 RDF sub-domains (Vitae, 2010).

Undertaking this thesis has provided a framework for me to reflect on my past contribution to research and to consider my future direction. In the short term, I will continue to co-lead the feasibility study (publication 7) to completion in early 2021. In the meantime, I am developing the draft protocol and processes for the international CRPS clinical research registry. The final protocol will be informed by the findings of publication 7. I will continue to lead the clinical trial within a Versus Arthritis-funded research programme (p.76). This includes co-designing the protocol, submission of ethical and regulatory approvals and overseeing the delivery of the study. I will build on my connections with UWE and would like to seek out opportunities to teach on research modules and supervise doctoral students.

In the longer term, I am committed to a clinical research career in the field of chronic pain and in particular CRPS. I look forward to building on my work to date and leading applications to funding bodies, supervising higher degree students

and consolidating the skills I have gained as an independent researcher. As a nurse, I remain keen to support others within my profession to follow a clinical academic pathway.

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Appendix 1: Publications 1- 8

Appendix 2: Doctoral descriptors at UWE

The award of a doctorate at UWE Bristol requires the postgraduate researcher to demonstrate that they:

- have conducted enquiry leading to the creation and interpretation of new knowledge through original research or other advanced scholarship, shown by satisfying scholarly review by accomplished and recognised scholars in the field;
- can demonstrate a critical understanding of the current state of knowledge in that field of theory and/or practice;
- show the ability to conceptualise, design and implement a project for the generation of new knowledge at the forefront of the discipline or field of practice including the capacity to adjust the project design in the light of emergent issues and understandings;
- can demonstrate a critical understanding of the methodology of enquiry;
- have developed independent judgement of issues and ideas in the field of research and / or practice and are able to communicate and justify that judgement to appropriate audiences;
- can critically reflect on their work and evaluate its strengths and weaknesses including understanding validation procedures.

Appendix 3: Email confirming permission to use the RDF

Website Vitae <website@vitae.ac.uk>
Tue 3/5/2019 11:03 AM

Sharon Grieve;

Website Vitae <website@vitae.ac.uk>

Hi Sharon
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Let me know if you have any questions.

Kind regards

David [redacted]
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Appendix 4: RDF sub-domains achieved in publications 1-8

RDF Sub-domain achieved	Descriptor	Publication							
		1	2	3	4	5	6	7	8
A1: Knowledge base	Subject knowledge	**X**[a]	x[b]	x	x	x	x	x	x
	Research methods: theoretical knowledge		**X**	x	x	x	x	x	x
	Research methods: practical application		**X**	x	x	x	x	x	x
	Information seeking	**X**	x		x	x	x	x	x
	Information literacy and management	**X**	x	x	x	x	x	x	x
	Languages							**X**	
	Academic literacy and numeracy	**X**	x	x	x	x	x	x	x
A2: Cognitive abilities	Analysing		**X**	x	x		x		x
	Synthesising			**X**	x		x		x
	Critical thinking			**X**	x		x	x	x
	Evaluating				**X**	x	x	x	x
	Problem solving			**X**			x	x	
A3: Creativity	Inquiring mind		**X**	x	x		x	x	x
	Intellectual insight			**X**	x		x	x	x
	Innovation		**X**				x	x	
	Argument construction						**X**		x
	Intellectual risk						**X**		
B1: Personal qualities	Responsibility				**X**	x	x	x	x
	Self-reflection				**X**		x	x	x
	Enthusiasm				**X**		x	x	x
	Perseverance				**X**	x	x	x	x
	Integrity		**X**		x	x	x	x	x
	Self-confidence		**X**		x		x	x	x
B2: Self-management	Responsiveness to change						**X**	x	x
	Commitment to research					**X**	x	x	x
	Preparation and prioritisation	**X**	x	x	x	x	x	x	x
	Time management	**X**	x		x	x	x	x	x
	Work-life balance						**X**	x	x
B3: Professional and career development	Networking		**X**	x	x	x	x	x	x
	Responsiveness to opportunities[c]								
	Continuing professional development[c]								
	Career management[c]								
	Reputation and esteem				**X**	x	x	x	x
C1: Professional conduct	Ethics, principles and sustainability		**X**		x		x	x	x
	Health and safety		**X**		x	x	x	x	x
	Legal requirements				**X**		x	x	x

	Descriptor	Publication							
		1	2	3	4	5	6	7	8
	IPR and copyright				**X**	x	x	x	x
	Respect and confidentiality				**X**	x	x	x	x
	Attribution and co-author				**X**	x	x	x	x
	Appropriate practice				**X**	x	x	x	x
C2: Research management	Project planning and delivery				**X**	x	x	x	x
	Research strategy						**X**	x	x
	Risk management				**X**			x	x
C3: Finance, funding and resources	Income and funding generation						**X**	x	
	Financial management						**X**	x	
	Infrastructure and resources						**X**	x	
D1: Working with others:	Team working	**X**	x	x	x	x	x	x	x
	Influence and leadership						**X**	x	x
	Collegiality						**X**	x	x
	Supervision				**X**			x	x
	Mentoring				**X**			x	x
	People management						**X**	x	x
	Equality and diversity							**X**	x
	Collaboration	**X**	x	x			x	x	x
D2: Communication and dissemination	Communication methods				**X**	x	x	x	x
	Publication	**X**	x	x	x	x	x	x	x
	Communication media			**X**			**X**	x	x
D3: Engagement and impact	Public engagement				**X**		x	x	
	Global citizenship						**X**	x	x
	Teaching						**X**		x
	Enterprise						**X**		
	Policy						**X**		
	Society and Culture						**X**		

[a] Descriptors in bold are newly acquired
[b] Descriptors in regular font are existing, and developed further via the publication
[c] Acquired via continuous professional development

Appendix 5: Poster from the British Pain Society Annual Scientific Meeting 2015

Royal National Hospital for Rheumatic Diseases

University of the West of England, BRISTOL

Royal United Hospitals Bath NHS Foundation Trust

What outcome measures are being used in Complex Regional Pain Syndrome clinical trials? A systematic literature review

Grieve, S [1,2], Jones, L [2], Walsh, N [2], McCabe, C [1,2]

[1]Royal National Hospital for Rheumatic Diseases, Bath, UK; [2] University of the West of England, Bristol, UK

Background

- Complex Regional Pain Syndrome (CRPS) is a chronic pain condition which predominantly occurs after limb trauma.
- Currently, synthesis of clinical trial evidence is limited as there is no standardised core measurement set of internationally agreed outcome measures.
- Identifying the outcome measures currently used in clinical trials will inform the development of a shared core measurement set of internationally agreed outcome measures.

Aims

- To conduct a systematic literature review to identify patient or health professional reported outcome measures in a questionnaire format, used in CRPS specific clinical trials since 2000.
- To determine which of these have been developed and psychometrically tested in a CRPS population.

Method

- A systematic search of electronic databases EMBASE, Medline, PsycInfo, CINAHL and LILACS was conducted identifying literature from 2000 – April 2014
- No restrictions were placed on study design or quality as the intention was to capture all questionnaire outcome measures used for CRPS clinical trials regardless of methodology. (See Table 1 for inclusion criteria)
- Papers available in full text were examined and questionnaire outcome measures were identified.
- Objective clinical measures were not captured for the purposes of this review.
- The outcome measures identified were mapped to the six core Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) domains[2] to inform the future selection of a final core measurement set (Table 2)

Table 1: Inclusion Criteria

Inclusion Criteria
English language
Primary data
Adult population
Evaluating an intervention directed at CRPS

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Results

- 104 full text papers were included in the review (Figure 1)
- 68 patient or health professional reported questionnaire outcome measures identified.
- Papers were classified according to the three core elements of CRPS treatment[1]; pain management (n=82), rehabilitation (n=22) and psychological therapy (n=0).
- Four measures were adapted specifically for CRPS.
- 64 outcome measures were generic.

Figure 1: Selection of studies

- Health professional reported outcome measures comprised only 9% of those identified.
- Five outcome measure questionnaires were validated for CRPS:
  - Radboud Skills
  - Rising and Sitting
  - Walking Stairs
  - Walking Ability
  - Neuropathic Pain Scale.

Table 2: IMMPACT Domains

IMMPACT domain	Outcome measures (n)
Pain	19
Physical Functioning	29
Emotional functioning	10
Participant ratings of global improvement and satisfaction with treatment	8
Symptoms and adverse events	1
Participant disposition	0

Conclusion

- Currently CRPS clinical trials use a broad range of patient reported outcome measures to evaluate the impact of interventions for CRPS.
- Many measures are not psychometrically tested in the CRPS population.
- The diversity of outcome measures used across the studies demonstrates a clear need for the development of a core measurement set to be used in CRPS clinical trials.

1. O'Connell NE et al. (2013) Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database of Systematic Reviews 4

2. Turk et al. (2003) Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 106(3): 337-345