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Towards development of core domain sets for short term and long term studies of calcium pyrophosphate crystal deposition (CPPD) disease: A framework paper by the OMERACT CPPD working group

Ken Cai^{a,*}, Amy Fuller^{b,c}, Yiling Zhang^a, Owen Hensey^d, David Grossberg^{e,f}, Robin Christensen^g, Beverley Shea^h, Jasvinder A. Singh^{i,j,k}, Geraldine M. McCarthy^l, Ann K. Rosenthal^m, Georgios Filippouⁿ, William J. Taylor^o, Cesar Diaz-Torne^p, Lisa K. Stamp^q, N. Lawrence Edwards^r, Tristan Pascart^s, Fabio Becce^t, Sabrina M. Nielsen^g, Peter Tugwell^u, Dorcas Beaton^v, Abhishek Abhishek^{b,c}, Sara K. Tedeschi^w, Nicola Dalbeth^a

^a Bone and Joint Research Group, Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, 85 Park Road, Auckland, New Zealand

^b Academic Rheumatology, University of Nottingham, Nottingham, United Kingdom

^c Nottingham NIHR-BRC, Nottingham, United Kingdom

^d The Central Remedial Clinic, Dublin, Ireland

^e Holy Cross Hospital, Silver Spring, MD, United States

^f Suburban Hospital, Bethesda, MD, United States

^g Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen & Research Unit of Rheumatology,

Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark

^h Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

ⁱ Medicine Service, VA Medical Center, Birmingham, AL, United States

^j Department of Medicine at the School of Medicine, University of Alabama at Birmingham (UAB), Birmingham, AL, United States

^k Department of Epidemiology at the UAB School of Public Health, Birmingham, AL, United States

^l University College Dublin, Dublin, Ireland

^m Department of Medicine, Medical College of Wisconsin, Milwaukee, United States

ⁿ Rheumatology Unit, ASST-Fatebenefratelli L, Sacco University Hospital, University of Milan, Italy

^o Department of Medicine, University of Otago, Wellington, New Zealand

^p Department of Rheumatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain

^q Department of Medicine, University of Otago, Christchurch, New Zealand

^r Department of Medicine, University of Florida College of Medicine, Gainesville, Florida, United States

^s Department of Rheumatology, Hospital Saint-Philbert, Lille Catholic University, Lille, France

^t Department of Diagnostic and Interventional Radiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

^u Department of Medicine, University of Ottawa, Ottawa, Canada

^v Institute for Work and Health, University of Toronto, Toronto, Canada

^w Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, Boston, MA, United States

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ABSTRACT

Introduction: Although calcium pyrophosphate deposition (CPPD) is common, there are no published outcome domains or validated measurement instruments for CPPD studies. In this paper, we describe the framework for development of the Outcome Measures in Rheumatology (OMERACT) CPPD Core Domain Sets.

Methods: The OMERACT CPPD working group performed a scoping literature review and qualitative interview study. Generated outcomes were presented at the 2020 OMERACT CPPD virtual Special Interest Group (SIG) meeting with discussion focused on whether different core domain sets should be developed for different calcium pyrophosphate deposition (CPPD) clinical presentations and how the future CPPD Core Domain Set may overlap with already established osteoarthritis (OA) domains. These discussions informed development of a future work plan for development of the OMERACT CPPD Core Domain Sets.

Findings: Domains identified from a scoping review of 112 studies and a qualitative interview study of 36 people (28 patients with CPPD, 7 health care professionals, one stakeholder) were mapped to core areas of OMERACT Filter 2.1. The majority of SIG participants agreed there was need to develop separate core domain sets for “short term” and “long term” studies of CPPD. Although CPPD + OA is common and core domain sets for OA have been established, participants agreed that existing OA core domain sets should not influence the

* Corresponding author.

E-mail address: k.cai@auckland.ac.nz (K. Cai).

development of OMERACT core domain sets for CPPD. Prioritization exercises (using Delphi methodology) will consider 40 potential domains for short term studies of CPPD and 47 potential domains for long term studies of CPPD.

Conclusion: Separate OMERACT CPPD Core Domain Sets will be developed for “short term” studies for an individual flare of acute CPP crystal arthritis and for “long term” studies that may include participants with any clinical presentation of CPPD (acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and/or CPPD + OA).

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Introduction

Calcium pyrophosphate deposition (CPPD) disease is a clinical manifestation of calcium pyrophosphate (CPP) crystal deposition, an umbrella term that includes acute CPP crystal arthritis (also known as “pseudogout”), chronic CPP crystal inflammatory arthritis, and CPPD with osteoarthritis (OA) (CPPD + OA) [1,2]. Although CPPD is common [3], it is understudied and there are no published outcome domains or validated measurement instruments for CPPD disease [4]. The OMERACT CPPD Working Group formed in 2018 to develop a core domain set for CPPD.

There are challenges to defining CPPD clinical outcomes, as this condition has diverse clinical presentations including single or recurrent flares of acute CPP crystal arthritis, often with long asymptomatic periods [5], chronic inflammatory arthritis, and/or CPPD + OA (Figure 1). While some sites are typically involved (knee and wrist), other locations in the peripheral and axial skeleton may be affected. CPPD strongly associates with OA, which in some patients is characterized by an atypical distribution of joint involvement compared to OA without CPPD; herein we refer to this co-occurrence as CPPD + OA as recommended in the EULAR terminology [6].

There have been very few clinical trials including patients with CPPD as an explicit condition, reflecting an underappreciation of the clinical significance of this common crystalline arthritis. Challenges to CPPD clinical trials also include the diversity and complexity of the condition, the lack of universally accepted classification criteria, a virtually non-existent drug development pipeline despite a good understanding of its pathophysiology, and the lack of validated outcomes measures. However, future studies may test novel anti-inflammatory agents for treating acute CPP arthritis flares and long-term therapies to prevent recurrent flares. Future development of therapies that target, inhibit, or reverse CPP crystal formation and deposition would be of great interest for all manifestations of CPPD and could have profound impact. Such trials would be greatly facilitated by agreement on relevant outcome domains and instruments for measurement. In this paper, we describe the framework for development of the Outcome Measures in Rheumatology (OMERACT) CPPD Core Domain Sets.

Methods

The OMERACT CPPD Working Group comprises clinicians, researchers, methodologists and patient research partners [7]. In accordance with OMERACT methodology [8], we identified that there were no pre-existing core outcome sets for CPPD in the literature and developed a plan to address this. Based upon the EULAR definitions for CPPD clinical presentations [2] we structured our Population, Intervention, Comparator, Outcome and Context (PICOC) question for adults with CPPD (Table 1).

First, we developed and implemented a protocol for a scoping literature review of outcome domains reported in published CPPD clinical studies (PROSPERO CRD: 42019137075; 09-07-2019). Reported outcomes were mapped to core areas and domains of OMERACT Filter 2.1 [8] and categorized by CPPD clinical presentation [9]. We then developed a protocol for a qualitative interview study involving semi-structured interviews of people with CPPD, their caregivers, healthcare professionals, and other stakeholders to identify further outcome domains relevant to their experience and knowledge of CPPD and complement those in the scoping review. These interviews were conducted across three continents and six countries and the results of this study have recently been published [10]. Similar to the scoping review, identified domains were mapped to OMERACT Filter 2.1 and categorised by CPPD clinical presentation for interviews with patients. As all mapped domains have been described in detail previously [9,10], in this paper, we present the most frequently mapped outcome domains from the scoping review of CPPD studies and a qualitative interview study of patients with CPPD.

At the CPPD virtual SIG meeting in October 2020, we presented the outcome domains identified from the scoping literature review and qualitative study. Prior to the meeting, registered participants were invited to review an introductory presentation about CPPD, two recorded video interviews with our CPPD patient research partners, and a written summary of the research completed so far by the CPPD Working Group [7]. Following a short introductory presentation, discussion was focused to consider the two key issues: [1] whether different core domain sets should be developed for different CPPD

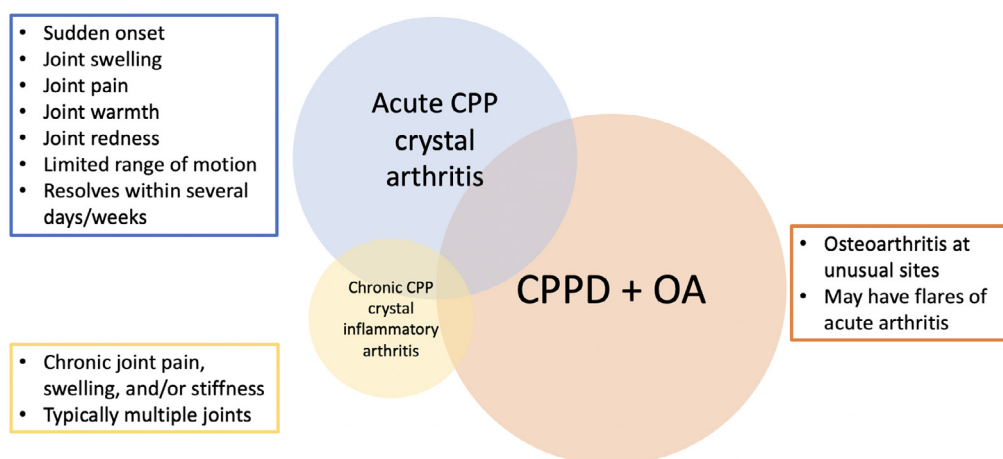


Fig. 1. CPPD clinical presentations and manifestations

Table 1
PICOC question for the CPPD core domain set

Component of PICOC	Description
Population	Adults with CPPD
Intervention	Any intervention: includes, but is not limited to medical therapy (including NSAIDs, colchicine, prednisone (including intra-articular injections), interleukin (IL)-1 inhibitors, inflammasome inhibitors, disease modifying anti-rheumatic drugs, crystal-dissolving therapies), radiosynovectomy, surgical therapy, behavioral, educational, complementary and alternative medicines
Control	Placebo, active comparator, usual care
Outcome	Core Domain Set under development
Context (Setting)	Clinical studies including randomized controlled trials setting (for both short and long-term management)

CPPD, Calcium Pyrophosphate Deposition; NSAID, Non-Steroidal Anti-Inflammatory Drug

clinical presentations and, [2] how the group should manage the overlap with already established OA domains [11,12].

Following the SIG meeting and based upon the aforementioned work, the OMERACT CPPD Working Group has developed a work plan to develop the OMERACT CPPD Core Domain Sets according to the OMERACT Core Domain Set workbook.

Results

Summary of the scoping review and qualitative study

The results of the scoping literature review and qualitative study have been reported in full [9,10]. There were substantial differences between the most frequently mapped domains in the scoping review and the qualitative study (Figure 2).

The scoping review identified 112 studies [9]. The predominant CPPD clinical presentations were CPPD + OA (47 studies), acute CPP crystal arthritis (24 studies) and chronic CPP crystal inflammatory arthritis (7 studies). In 21 studies, the predominant CPPD clinical presentation was unclear. The reported outcomes were mapped to core areas and domains of the OMERACT Filter 2.1. The most frequently mapped outcome domains within the core area of Manifestations/Abnormalities were joint damage on imaging tests (59 studies), joint calcification on imaging tests (28 studies) and joint pain (26 studies). Within the core area of Life Impact, the most frequently reported outcome domains were response to treatment (23 studies) and overall

function (14 studies) [9]. Very few studies had outcomes mapped to the core areas of Longevity or Societal/Resource Use.

The qualitative interview study included 36 interviews involving 28 patients (of which six included a caregiver), seven health care professionals and one stakeholder from a non-profit arthritis-focused organization [10]. The patients represented a range of CPPD clinical presentations and many participants had more than one CPPD clinical presentation: 21 had acute CPP crystal arthritis, 9 had chronic CPP crystal inflammatory arthritis and 21 had CPPD + OA. For patients with CPPD, the most frequently mapped outcome domains within the core area of Manifestations/Abnormalities were joint pain (n=28), joint swelling (n=23), joint stiffness (n=23), joint movement (n=19) and acute CPP crystal arthritis flares (n=19). Within the core area of Life Impact, the most frequently mapped outcome domains were overall function (n=27) and emotional or psychological wellbeing (n=9). Within Societal/Resource Use, the most frequently mapped outcome domains were use of analgesics (n=23). No outcome domains were mapped to Longevity.

Overlap with OA

In both the scoping literature review and qualitative interview study, the most common CPPD clinical presentations were CPPD + OA [9,10]. CPPD + OA was the predominant clinical presentation in 42% of previous CPPD studies (47 of 112 studies) and present in 75% of patients interviewed (21 of 28 patients). In previous studies of CPPD + OA, the most commonly mapped domains excluding imaging manifestations included joint pain (14 studies), overall function (10 studies), joint stiffness (5 studies) and need for joint surgery (5 studies). In contrast, the most commonly mapped domains from interviews of patients with CPPD + OA, were joint pain (21 patients), overall function (21 patients), use of analgesics (17 patients) and joint swelling (16 patients). Similar to the established OA core domain sets for hip/knee OA [12] and hand OA [11], pain and physical function were the most commonly reported domains for the clinical presentation of CPPD + OA from clinical studies and patients.

Summary of the SIG meeting

There were 35 participants (51% women) at the virtual SIG meeting including five patient research partners. The majority of participants were clinicians and/or researchers (30 [86%]). The majority of participants supported developing unique core domain sets for different CPPD clinical presentations. There was general agreement to

Scoping Review of CPPD Studies (n=112 papers)	Interview Study of Patients with CPPD (n=28 patients)
Joint damage on imaging tests (53%)	Joint pain (100%)
Joint calcification on imaging tests (25%)	Overall function (96%)
Joint pain (23%)	Use of analgesics (82%)
Response to treatment (21%)	Joint swelling (82%)
Side effects of treatment (13%)	Joint stiffness (75%)
Overall function (13%)	Joint movement (68%)
Joint swelling (11%)	Acute CPP crystal arthritis flares (68%)
Inflammation in blood or joint fluid (ESR or CRP) (11%)	Related medical conditions such as osteoarthritis (50%)
Joint movement (10%)	Emotional or psychological well-being (32%)
Related medical conditions such as osteoarthritis (8%)	Side effects of treatment (32%)

Core Area: Manifestations/Abnormalities Life Impact Longevity Societal/Resource Use

Fig. 2. Most frequently mapped outcome domains from the scoping review of clinical studies of CPPD (n=112 papers) and the qualitative interview study of patients with CPPD (n=28 patients).

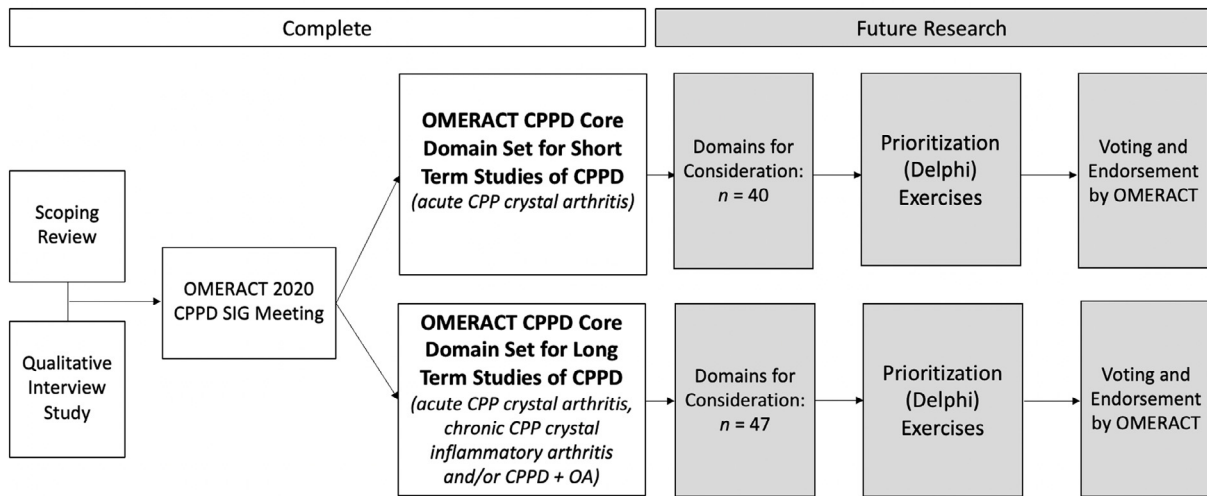


Fig. 3. Framework for development of the OMERACT CPPD core domain sets

separate the Core Domain Sets for different CPPD clinical presentations into “acute” and “chronic” outcomes. These align to “short term” studies for an individual flare of acute CPP crystal arthritis and for “long term” studies of CPPD that may include participants with any clinical presentation of CPPD (flares of acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and/or CPPD + OA). Some participants raised concerns that separating the different CPPD clinical presentations may not capture the heterogeneity of CPPD, particularly as many people with this condition have more than one form over the course of a lifetime, sometimes occurring simultaneously, which may affect recruitment for future CPPD clinical studies. However, the “long term” CPPD core outcome domain would include participants with the full spectrum of clinical presentations including recurrent acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and/or CPPD + OA. Following a vote, 76% (22/29) of voting participants answered “yes” to developing different core domain sets for acute and chronic CPPD clinical presentations.

Participants agreed that currently established OA domains should not impact the development of core domains for CPPD. Multiple participants highlighted that OA is a common co-morbid condition in many rheumatic conditions (such as rheumatoid arthritis) and considered a potentially relevant contextual factor that could be evaluated in subgroup analyses in CPPD studies. It was suggested that reporting of OA domains for subgroup analysis could be recommended for all future long-term CPPD studies.

Based upon the scoping review, qualitative interview study and discussion from the SIG meeting, the OMERACT CPPD Working Group formulated a workplan according to the OMERACT Core Domain Set workbook (Figure 3). Two separate Core Domain Sets will be developed for “short term” and “long term” studies of CPPD. We will use Delphi methodology to prioritise domains for short term and long term CPPD studies, with the aim to present the preliminary CPPD Core Domain Sets for voting and endorsement by OMERACT.

Selection and prioritization of domains for the OMERACT CPPD core domain sets

In accordance with OMERACT methodology [8], the next stage of work towards development of the CPPD Core Domain Sets focuses on the selection and prioritization of domains using Delphi methodology. We aim to survey 100 patients with CPPD and 100 other stakeholders (total of 200 participants) utilising the network of patients

and stakeholders accessible to members of the OMERACT CPPD Working Group and the wider OMERACT community. Three rounds and a wrap up round will be performed with responses recorded and analysed using the Core Outcome Measurement in Effectiveness Trials (COMET) DelphiManager software, which has been modified for OMERACT.

Our qualitative work and literature reviews have generated 40 domains for consideration across four core areas for short-term studies of an individual flare of acute CPP crystal arthritis and 47 domains for consideration across the four core areas for long-term studies of CPPD. As the domains of adverse events including death are mandatory in all clinical trials [13], these domains were not included for consideration. Based on our previous qualitative work, definitions have been created for each domain to clarify its scope and meaning [10]. The domains and the core area they represent are shown in Supplementary Table 1 and 2.

Discussion

This paper outlines the framework for development of the OMERACT CPPD Core Domain Sets. Even though CPPD is common, very few clinical trials have been conducted in CPPD and there are no published outcome domains or validated measurement instruments for CPPD studies. We have mapped the reported outcomes from our scoping review and qualitative study to domains and core areas of the OMERACT Filter 2.1. Following a collaborative, virtual SIG meeting involving clinicians, researchers and patient research partners, we have developed a workplan for prioritization (Delphi) exercises and eventually voting on our core domain sets.

We recognized two key issues that required clarification before proceeding to the prioritization exercises. CPPD is a heterogeneous condition with different clinical presentations and patients can experience more than one clinical presentation(s) concurrently or over time. Of the 28 people with CPPD interviewed in our qualitative study, 21 had at least one episode of acute CPP crystal arthritis, 9 had chronic CPP crystal inflammatory arthritis, and 21 had CPPD + OA [10]. We decided the simplest method to address this issue is to develop separate core domain sets for short-term studies of people with CPPD and the range of clinical presentations. We estimate the duration of “short term” CPPD studies (for an individual flare of acute CPP crystal arthritis) to be over the period of the flare, typically 1–2 weeks and for “long term” CPPD studies (any

presentation of CPPD including acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and/or CPPD + OA) to be months or even years. A similar approach has been utilized in gout, where there are separate ‘acute’ and ‘chronic’ core domain sets [14]. However, while the approach may be similar, there are currently limited treatment options for people with chronic CPPD including no disease modifying or crystal dissolving therapies [15]. Although CPPD + OA is common and there are already established core domain sets for OA [12], we decided this should not impact the development of the OMERACT Core Domain Sets for CPPD.

With these issues clarified, the CPPD Working Group will commence prioritization work with Delphi exercises which will lead to the formation of the preliminary core domain sets for “short term” studies for an individual flare of acute CPP crystal arthritis and for “long term” studies of CPPD that may include participants with any clinical presentation of CPPD (acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and/or CPPD + OA), in accordance with OMERACT methodology [8]. We aim to present the CPPD Core Domain Sets for voting and endorsement by OMERACT.

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Declaration of Competing Interest

KC reports a research fellowship grant from Arthritis Australia. RC is a member of the Technical Advisory Group of OMERACT. JAS has received consultant fees from Crealta/Horizon, Medisys, Fidia, PK Med, Two labs Inc, Adept Field Solutions, Clinical Care options, Clearview healthcare partners, Putnam associates, Focus forward, Navigator consulting, Spherix, MediQ, Jupiter Life Science, UBM LLC, Trio Health, Medscape, WebMD, and Practice Point communications; and the National Institutes of Health and the American College of Rheumatology. JAS owns stock options in TPT Global Tech, Vaxart pharmaceuticals and Charlotte’s Web Holdings, Inc. JAS previously owned stock options in Amarin, Viking and Moderna pharmaceuticals. JAS is on the speaker’s bureau of Simply Speaking. JAS is a member of the executive of OMERACT. DG has a private equity holding in Charlotte’s Web Holdings, Inc. ND reports grants and personal fees from AstraZeneca, grants from Amgen, personal fees from Dyve, personal fees from Hengrui, personal fees from Selecta, personal fees from Horizon, personal fees from Abbvie, personal fees from Pfizer, personal fees from Janssen, personal fees from Arthroci, outside the submitted work. AA and SKT have received consultant fees from NGM Biopharmaceuticals. FB has received personal consultant fees from Horizon Therapeutics. OMERACT, an organization that develops outcome measures in rheumatology, receives arms-length funding from 8 companies. The other authors have no disclosures.

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Author Contributions

KC and ND (the guarantors) accept full responsibility for the work and controlled the decision to publish. KC interpreted the data and completed the original draft of the manuscript. All authors revised and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2021.04.019.

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