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Core domain set for chronic and/or recurrent manifestations of calcium pyrophosphate deposition disease: OMERACT delphi survey to establish consensus

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ABSTRACT

Objective: To agree on important domains for the Outcome Measures in Rheumatology (OMERACT) core domain set for chronic and/or recurrent manifestations of calcium pyrophosphate deposition (CPPD) disease.
Methods: Patient research partners (PRPs) and other participants (mainly clinicians and researchers) contributed to three rounds of a consensus survey using Delphi methodology. Consensus was defined if ≥70% of both patients and other participants scored the domain as 'critically important domain to include'. In a subsequent ranking exercise, all participants were asked to select and rank up to 10 of the domains reaching consensus.

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Results: Fifteen domains reached consensus as critically important. Within the Pathophysiological Manifestations area, these were joint pain, joint tenderness, joint swelling, acute CPP crystal arthritis flare, joint damage on imaging tests, joint calcification on imaging tests, and crystals in joint fluid. Within the Life Impact area, these were overall function, ability to complete daily tasks, ability to work, health related quality of life, patient global assessment response to treatment, patient global assessment of disease activity, physician global assessment of disease activity, and patient satisfaction with treatment. No domains within the Societal/Resource Use area reached consensus as critically important. In the ranking exercise, joint pain, joint tenderness, joint swelling, acute CPP crystal arthritis flare and overall function were most highly ranked.
Conclusion: This work has identified potential domains for the OMERACT core domain set for chronic and/or recurrent manifestations of CPPD disease. There was strong support for joint pain, joint tenderness, joint swelling, acute CPP crystal arthritis flare, overall function, and global assessments of disease activity as core domains.

Introduction

Calcium pyrophosphate deposition (CPPD) disease is a common form of inflammatory arthritis caused by the deposition of calcium pyrophosphate (CPP) crystals [1]. It mainly affects older adults and presents with a wide spectrum of clinical manifestations. The European Alliance of Associations for Rheumatology (EULAR) CPPD task force has recognised a range of clinical manifestations including acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and CPPD with osteoarthritis (OA) [2]. The American College of Rheumatology (ACR) and EULAR have developed a validated classification criteria for CPPD disease, allowing for consistent selection of patients into CPPD studies [3].

Further studies on the treatment of CPPD disease are much needed as current treatment recommendations are based on low-level evidence, and several trials of treatments for chronic CPPD manifestations are about to be launched [4]. Given the varied manifestations of CPPD disease presentation, and general lack of trials in CPPD disease to date, it has been challenging to agree upon or validate outcome measures for studies of CPPD disease. The Outcome Measures in Rheumatology (OMERACT) CPPD working group (WG) was formed to develop an OMERACT core domain set for CPPD disease. The steering committee for this work, comprising of five clinicians/researchers, two OMERACT methodologists, two patient research partners (PRPs) and one fellow (three members from the Asia Pacific region, three members from Europe, four members from North America), has followed the OMERACT process closely for domain selection outlined in the OMERACT handbook [5]. This WG has undertaken work to identify potential core domains through a scoping literature review and qualitative research [6,7]. The steering committee has presented the progress of their work periodically to the wider WG for feedback. In response to this work, a framework for development of a CPPD core domain set was established at the 2020 OMERACT CPPD virtual Special Interest Group (SIG) meeting [8]. The meeting attendees agreed on the need to develop two separate CPPD core domain sets, one for studies focused on an individual flare of acute CPP crystal arthritis and another for studies that may include people with any other clinical presentations of CPPD disease (which may include recurrent flares of acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and/or CPPD + OA).

Herein, we describe the next steps in the OMERACT core domain set development, which involved a consensus exercise to identify potential domains for the OMERACT core domain set. In this manuscript we report the results of the Delphi survey combined with the subsequent ranking exercise to prioritize the domains for the OMERACT core domain set for chronic and/or recurrent manifestations of CPPD disease.

Methods

This Delphi study was conducted following the methodology outlined in the Core Domain Selection Process chapter of the OMERACT Handbook [5]. The study was approved by the Auckland Health Research Ethics Committee (ref AH23039). All participants consented to participate in the study at registration. This study is reported according to ACCORD (ACcurate COnsensus Reporting Document) [9].

The survey was constructed and managed using DelphiManager (University of Liverpool), modified for OMERACT. The CPPD steering committee worked closely with OMERACT senior methodologists to build the Delphi survey. Through prior work, 47 candidate domains were identified by the CPPD OMERACT WG's scoping review and patient/caregiver qualitative studies [6,7,10]. Potential domains and their definitions were reviewed and modified by the steering committee to determine the 32 final candidate domains included in round 1 of the survey. Candidate domains were grouped into the OMERACT core areas of Pathophysiological Manifestations, Life Impact, and Societal/Resource Use [11]. Supplementary table 1 shows the definitions of the candidate domains provided to the participants in round 1.

Recruitment of potential participants was aimed internationally at interested patients affected by CPPD disease (PRPs) and clinicans, researchers, public providers, purchasers, payers, policy makers, product makers and investigators (other participants). Advertisements of the survey were circulated among the Gout and Crystal Arthritis Network (G-CAN), other crystal disease networks, rheumatology clinician associations, arthritis charitable trusts, social media support groups, clinicians and patients at participating local hospitals. Members of the working group were also invited to participate in the survey. No reimbursement was offered to study participants.

There were three rounds of the Delphi survey followed by a ranking exercise. In each round, participants were given an introduction to CPPD with 'a two year clinical trial comparing specialist nurse led care with standard care in patients with CPPD disease' provided as an example of a study of chronic and/or recurrent manifestatations of CPPD disease. Notification of each round was sent to the email address provided by the participant at registration. For the three rounds of the Delphi survey, participants were asked to rate the importance of each domain on a 1–9 point scale (1–3 indicating 'not important', 4–6 indicating 'important but not critical', 7–9 indicating 'critically important domain to include'). During round 1 only, participants were asked to nominate additional domains. Nominated additional domains were reviewed by the steering committee and decisions were made regarding inclusion into round 2. For rounds 2 and 3, participants could see their own previous ratings along with distribution of ratings from other participants. Participants could leave comments in all rounds.

Consistent with OMERACT's domain selection methodology [12], consensus that a domain was critically important was defined if $\geq$70 % of both PRPs and other participants scored the domain as 'critically important domain to include' (score 7–9) after two rounds of inclusion in the Delphi survey. Consensus that a domain was 'not important' was defined if $\geq$70 % of both participant groups scored the domain as 'not important' (score 1–3) after two rounds of inclusion in the Delphi survey. If a domain reached consensus as 'critically important domain to include' or 'not important' in round 2, it was removed from further rating in round 3. All domains were presented in at least two rounds for

voting.

Domains that reached consensus as 'critically important domain to include' were subsequently included in a ranking exercise. In the ranking exercise, participants were asked to rank up to 10 domains as their top choices for critically important domains to include and comment on the reasons for inclusion or exclusion.

Data were collected and recorded in de-identified format by DelphiManager. Analyses of the survey data were descriptive using counts, percentages, medians and interquartile ranges. Weighted percentages were calculated by averaging equally the percentage of the PRP group and the other participant group that rated candidate domains as critically important. The weighted percentages were used to generate separate bubble plots of different core areas that show the relative strength of agreement. The bubble plot comprises of the weighted percentages on the y-axis and the differences between the PRPs and other participants on the x-axis. Bubbles positioned on the right-hand side represent domains favoured more by PRPs, while bubbles on the left-hand side represent domains more favoured by other participants. The size of the bubble denotes weight of the domain votes with larger bubbles representing greater weight (many participants). Comments from all rounds of the survey were recorded against the relevant domain.

Results

Participant characteristics

The characteristics of 146 participants who registered for the Delphi survey are shown in Table 1. The majority of participants identified as female and European. Slightly under a quarter of participants were PRPs. Most participants were 40–59 years old. Twelve WG members completed all rounds of the Delphi survey and the ranking exercise.

Round 1 of the Delphi survey

Round 1 of the Delphi survey opened on 11 October 2022 and was completed by 138 participants, 94% response rate (Fig. 1). In round 1, four of 32 domains were already rated as critically important to include by ≥70% of both PRP and other participant groups. These domains and their equally weighted consensus percentages were joint pain (88%), acute CPP crystal arthritis flare (87%), overall function (79%), and joint swelling (75%) (Supplementary Table 2).

Participants nominated additional domains in round 1 that were reviewed by the steering committee. After committee review, five new domains and their definitions were included in round 2 survey (Supplementary Table 3). These domains were joint inflammation on imaging tests, ability to look after children, ability to commute to work, inpatient admission, and joint replacement surgery.

Table 1
Characteristics of registered study participants (n=146).

Sex, no. (%)	
Female	94 (64 %)
Male	52 (36 %)
Role, no. (%)	
Patient Research Partners	33 (23 %)
Other Participants[1]	113 (77 %)
• *Clinician*	96
• *Researcher*	46
• *Government organization representative*	5
• *Allied health professional*	4
• *Nurse*	3
• *Pharmaceutical representative*	1
• *Other*	8
Ethnicity, no. (%)	
European	72 (49 %)
White American	19 (13 %)
Other White	13 (9 %)
Black	7 (5 %)
Asian	14 (10 %)
Other	21 (14 %)
Age (years), no. (%)	
18–39	27 (18 %)
40–49	45 (31 %)
50–59	35 (24 %)
60–69	23 (16 %)
≥70	16 (11 %)

[1] Participants could select more than one role.

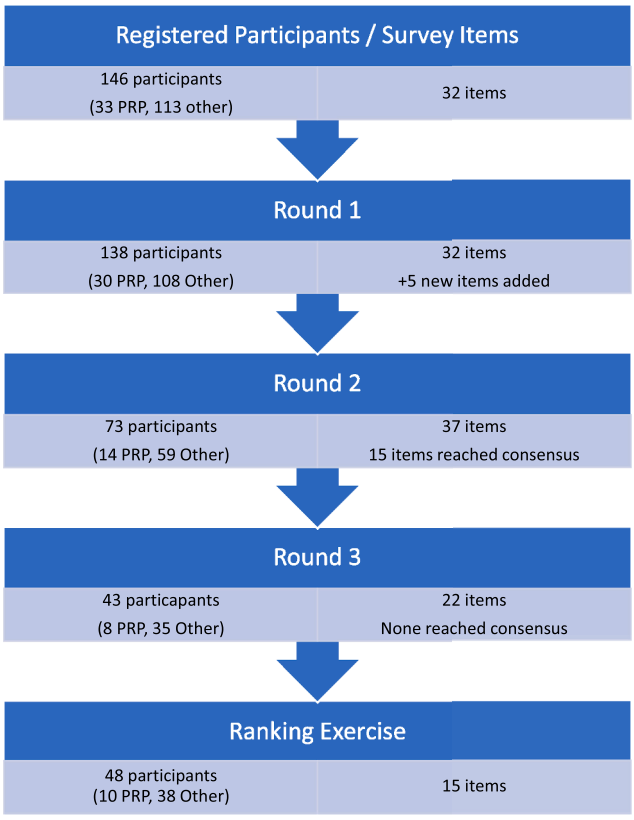

Fig. 1. Flow chart of participant completion of the Delphi survey. PRP: patient research partner.

Round 2 of the Delphi survey

Round 2 of the Delphi survey opened on 8 July 2023 and was completed by 73 participants (50% response rate). Fifteen of 37 domains reached consensus as critically important to include in round 2 (Table 2). These were all in the core areas of Pathophysiological Manifestations (n=7) or Life Impact (n=8). These domains and their weighted consensus percentages were joint pain (97%), acute CPP crystal arthritis flare (95%), overall function (93%), joint tenderness (89%), patient global assessment response to treatment (88%), joint damage on imaging tests (87%), joint swelling (86%), crystals in joint fluid (86%), health related quality of life (85%), patient global assessment of disease activity (82%), ability to complete daily tasks (81%), joint calcification on imaging tests (80%), physician global assessment of disease activity (79%), ability to work (77%), and patient satisfaction with treatment (74%).

In round 2, more than 90% of both PRPs and other participants agreed that joint pain, acute CPP crystal arthritis flare, and overall function were critically important domains to include in the core domain set. More than 85% of both PRPs and other participants agreed that joint damage on imaging tests, patient global assessment response to treatment, and joint swelling were critically important domains.

Table 2
Item consensus from sequential Delphi survey rounds. Proportion of patient research partners (PRPs) and other participants rating candidate domains as critical (7–9) for chronic and/or recurrent manifestations of CPPD disease. Domains achieving consensus by both PRPs and other participants are shown in bold.

Domain	Final round in Delphi exercise^	Patient research partners			Other participants			Equally weighted percentage#
		N	Count	%	N	Count	%	%
Pathophysiological Manifestations								
Joint pain	**2**	**14**	**14**	**100 %**	**59**	**55**	**93 %**	**97 %**
Joint tenderness	**2**	**14**	**14**	**100 %**	**59**	**46**	**78 %**	**89 %**
Joint swelling	**2**	**14**	**12**	**86 %**	**59**	**51**	**86 %**	**86 %**
Joint redness	3	8	0	0 %	35	1	3 %	2 %
Joint stiffness	3	8	6	75 %	35	9	26 %	51 %
Joint movement	3	8	8	100 %	35	22	63 %	82 %
Joint heat	3	8	0	0 %	35	0	0 %	0 %
Inflammation markers in blood	3	8	2	25 %	35	9	26 %	26 %
Inflammation markers in joint fluid	3	8	5	63 %	35	5	14 %	39 %
Acute CPP crystal arthritis flares	**2**	**14**	**13**	**93 %**	**59**	**57**	**97 %**	**95 %**
Joint damage on imaging tests	**2**	**14**	**12**	**86 %**	**59**	**52**	**88 %**	**87 %**
Joint calcification on imaging tests	**2**	**14**	**11**	**79 %**	**59**	**47**	**80 %**	**80 %**
Crystals in joint fluid	**2**	**14**	**13**	**93 %**	**59**	**46**	**78 %**	**86 %**
Joint inflammation on imaging tests*	3	8	6	75 %	35	24	69 %	72 %
Life Impact								
Overall function	**2**	**14**	**13**	**93 %**	**59**	**55**	**93 %**	**93 %**
Ability to complete daily tasks	**2**	**14**	**11**	**79 %**	**59**	**49**	**83 %**	**81 %**
Ability to do usual hobbies, leisure, exercise, and social activities	3	8	7	88 %	35	11	31 %	60 %
Ability to work	**2**	**14**	**11**	**79 %**	**59**	**44**	**75 %**	**77 %**
Balance	3	8	5	63 %	35	4	11 %	37 %
Reliance on support people	3	8	0	0 %	35	2	6 %	3 %
Health related quality of life	**2**	**14**	**11**	**79 %**	**59**	**53**	**90 %**	**85 %**
Sleep	3	8	7	88 %	35	4	11 %	50 %
Fatigue	3	8	7	88 %	35	3	9 %	49 %
Emotional or psychological wellbeing	3	8	4	50 %	35	4	11 %	31 %
Patients financial wellbeing	3	8	2	25 %	35	0	0 %	13 %
Patient global assessment response to treatment	**2**	**14**	**12**	**86 %**	**59**	**53**	**90 %**	**88 %**
Patient global assessment of disease activity	**2**	**14**	**11**	**79 %**	**59**	**50**	**85 %**	**82 %**
Physician global assessment of disease activity	**2**	**14**	**11**	**79 %**	**59**	**46**	**78 %**	**79 %**
Patient satisfaction with treatment	**2**	**14**	**10**	**71 %**	**59**	**45**	**76 %**	**74 %**
Adapting to physical disability	3	8	6	75 %	35	22	63 %	69 %
Ability to look after children*	3	8	2	25 %	35	7	20 %	23 %
Ability to commute to work*	3	8	3	38 %	35	10	29 %	34 %
Societal/Resource Use								
Direct cost	3	8	3	38 %	35	10	29 %	34 %
Indirect cost	3	8	2	25 %	35	5	14 %	20 %
Use of long-term medications	3	8	6	75 %	35	14	40 %	58 %
Inpatient admission*	3	8	4	50 %	35	23	66 %	58 %
Joint replacement surgery*	3	8	4	50 %	35	24	69 %	60 %

^ When consensus was achieved, data are shown from the round at which consensus was achieved.
# Equally weighted percentage is calculated by averaging percentage of PRPs and other participants.
* New domains added after round 1

Round 3 of the Delphi survey

Round 3 of the Delphi survey opened on 28 August 2023 and was completed by 43 participants (29% response rate). No further domains reached consensus as critically important to include in round 3 (Table 2). Eight domains were rated as critically important to include by ≥70% PRPs, but not by ≥70% of other participants. These were joint stiffness, joint movement, joint inflammation on imaging tests, ability to do usual hobbies, leisure, exercise, and social activities, sleep, fatigue, adapting to physical disability, and use of long-term medications. Throughout the three rounds of the survey, no domain reached consensus as not important. Supplementary Figure 1 shows the relative strength of agreement between PRPs and other participants.

Ranking exercise

The ranking exercise opened on 26 September 2023 and was completed by 48 participants (33% response rate). Table 3 shows the median ranking in the top 10 for the fifteen domains that reached consensus as critically important to include. All PRPs and more than 90% of other participants rated joint pain in their top 10 with median ranking of 1. Acute CPP crystal arthritis flare, joint tenderness, and joint swelling were also ranked highly among participants. Life impact domains were generally ranked lower with overall function reaching the highest median ranking of 5.

Participant comments

Participants gave reasons to support the domains that reached high level of consensus as critically important. Joint pain was described as an essential reason why a person with CPPD would need health care and a core manifestation of CPPD disease. Minimisation of joint pain was considered an important goal when treating chronic and/or recurrent manifestations of CPPD disease. Joint tenderness and joint swelling were also described as objective findings of joint inflammation that would respond to treatment. However, it was also noted that differentiating between joint tenderness in CPPD and osteoarthritis can be difficult, and that the joint tenderness domain may be similar to the joint pain domain. Control of acute CPP crystal arthritis flares was described as a key goal of long-term CPPD treatment. There was strong support for the overall function domain as an outcome of importance to patients. Participants considered that effective treatment should improve overall

Table 3
Top 10 ranking domains reaching consensus as critically important for chronic and/or recurrent manifestations of CPPD disease.

Domains reaching consensus after Round 3	Patient research partners (n=10) Median (IQR) ranking when ranked in the top ten	Other participants (n=38) Median (IQR) ranking when ranked in the top ten
	Pathophysiological Manifestations	
Joint pain	1 (1; 1)	1 (1; 2)
Joint tenderness	2 (2; 2)	2.5 (2; 5.75)
Joint swelling	3 (2.5; 3)	4 (3; 5)
Acute CPP crystal arthritis flare	2 (2;4)	2 (2; 4)
Crystals in joint fluid	9 (6; 9)	3.5 (1.75; 6)
Joint damage on imaging tests	7 (4; 9)	5 (4; 8)
Joint calcification on imaging tests	6 (4; 10)	5 (3; 7)
	Life Impact	
Overall function	5 (4.5; 6.5)	5 (4; 6)
Ability to complete daily tasks	5 (3.75; 5.25)	6.5 (4.25; 8)
Ability to work	6.5 (6; 7)	8 (7; 9)
Health related quality of life	7.5 (6.25; 8)	7 (5; 9)
Patient global assessment of response to treatment	8 (4.25; 8)	7 (5.75; 8.25)
Patient global assessment of disease activity	6 (4.5; 8.5)	6 (5; 8)
Physician global assessment of disease activity	5 (3.5; 7.5)	8 (6; 9)
Patient satisfaction with treatment	7.5 (6.25; 8.25)	7 (5; 9)

function.

Participants commented that joint damage on imaging tests was also an important domain for chronic and/or recurrent manifestations of CPPD studies as an objective measure of long-term structural damage and that a disease modifying treatment may affect this domain. Joint calcification and crystals in joint fluid were highlighted as having a key role in CPPD diagnosis, with a variable role as an outcome measure (critical if testing a product that is designed to produce crystal dissolution but less important if testing a symptom modifying therapy). There was general support for the patient-centred domains within the Life Impact area, particularly the patient global assessment of disease activity which was described as a key measure that captures the patient perspective of their condition and can change over time during long term treatment. Overlap between the Life Impact domains was noted by participants. For example, one participant noted the similarities between patient global response to treatment and patient satisfaction with treatment but considered that patient satisfaction with treatment may be preferable as this domain covers both effectiveness and adverse events.

Discussion

This work has provided important consensus and insights about the domains for chronic and/or recurrent manifestations on CPPD disease. Fifteen domains reached consensus as critically important to include in core domain set. Of these, joint pain, joint swelling, acute CPP crystal arthritis flare and overall function were the domains with the strongest consensus. Joint tenderness, joint damage on imaging tests, patient global assessment of response to therapy and patient global assessment of disease activity were also strongly endorsed by participants. These results will inform the development of the OMERACT core domain set for chronic and/or recurrent manifestations of CPPD disease.

The survey results align with prior research conducted by the OMERACT CPPD WG. In the previously conducted qualitative research, people with CPPD disease described that joint pain, joint swelling and loss of mobility were key symptoms impacting their daily life. Pain was identified as the central experience of CPPD that required effective treatment [10]. Acute CPP crystal arthritis flares were reported to be disabling and to have a significant negative psychological impact. Many participants reported impact on their overall function and ability to do daily activities [10]. Joint damage on imaging tests was a frequently reported outcome in the CPPD scoping review [6].

In this previous qualitative research, patients and carers also reported disruptions and limitations due to pain that affected all aspects of life [12]. This is reflected by the numerous Life Impact domains that reached consensus as critically important to include in the Delphi survey. Most of the Life Impact domains that reached consensus as critically important to include were broad and capture aspects of patient function, disease activity, quality of life, and response to treatment. There are similarities between many of the Life Impact domains included in the survey that may have caused some uncertainties for participants, particularly in the ranking exercise. For example, overall function and ability to complete daily tasks are similar constructs. Patient global assessment response to treatment and patient satisfaction with treatment are also similar constructs reflecting the patient's experience of treatment. These overlaps will need to be carefully considered when interpreting the survey results and constructing the core domain set.

PRPs were more likely to rate Life Impact domains as 'critically important' compared with other participants. There were eight domains that reached consensus with PRPs but not with other participants, most of which were in the Life Impact area. Other (non-patient) participants considered that even though most domains were important, some were not considered 'critical' for all studies. These differences reflect the challenges of identifying a core set of a small number of domains when CPPD disease affects many facets of a person's life. While not highly prioritized, consideration could be given to the final core domain set to capture a quality of life domain such as health related quality of life that is broad reaching and captures many of the aspects that patients consider critically important to include in the core domain set.

The sole aim of this Delphi survey was to identify important outcome domains to include in the OMERACT core onion, so instruments of measurement were not included in the candidate domain definitions. As a result, participants may have had different understandings of how each domain would be measured and that may have affected voting results. For example, 'joint tenderness' and 'joint swelling' could be interpreted as either patient or physician assessed. There will be subsequent work by the CPPD WG to address the best instruments for measurement, taking the domain definitions into consideration.

CPPD with OA is a recognised subset of CPPD disease [2], and there is an established OMERACT core domain set for hip and/or knee OA [13]. During the 2020 OMERACT CPPD disease SIG meeting, it was discussed that development of the CPPD disease core domains should occur independently of the existing OA core domains [8]. OA was viewed as a common comorbid condition and a potentially relevant contextual factor that could be evaluated in subgroup analyses in CPPD studies. OA core domains may be more relevant in these subgroup analyses.

The main strengths of this study include the significance of the research topic, the application of OMERACT standardised methodology, multi-national recruitment and the active involvement of PRPs throughout the study design and consensus building process. The previous scoping review showed substantial heterogeneity of reported domains between existing CPPD studies, underscoring the need for a core domain set that includes domains relevant to people with CPPD disease [6].

The main limitation was the high rate of loss to follow-up, coupled with the relatively low number of PRPs recruited. There were major delays in sending the second round of the Delphi survey due to software errors and delays rebuilding the survey. In addition, we experienced difficulty contacting participants after initial registration due to spam filters in institutional emails. It was also difficult to recruit PRPs, as

CPPD disease is not often correctly diagnosed and patient awareness of this condition may be low. Patients with CPPD disease often struggle with diagnostic delay and uncertainty around diagnosis [10], and CPPD disease patient support groups are not as well-established as other inflammatory arthritis support groups. Additionally, CPPD disease affects the older populations for whom completing a web-based survey may be a barrier to participation. The older, more comorbid population is less likely to participate in surveys, making it more challenging to recruit PRPs who are representative of the real life CPPD disease patient population [14]. To combat the loss of follow-up that was proportionally higher in the PRP group, results for PRP and other participants were reported separately for all rounds of the Delphi survey and then presented as equally weighted percentages. Reassuringly, most domains reached consensus early from round 1 and round 2.

At present, there are no agreed core domain sets for studies on CPPD disease and the lack of agreed core domains limits the quality of studies. This Delphi survey has identified fifteen potential core domains for chronic and/or recurrent manifestations of CPPD disease. Joint pain, joint tenderness, joint swelling, acute CPP crystal arthritis flare,overall function, and global assessments of disease activity have very strong support to be included in the core domain set. Joint damage on imaging tests and other patient-reported measures of Life Impact should also be considered as potential domains for the core domain set. Results from this work will directly inform the next steps in developing the OMERACT core domain set for chronic and/or recurrent manifestations of CPPD disease. Future development of validated outcome measures in CPPD disease will also be critical to advance clinical trials in this common crystal arthritis.

Declaration of competing interest

S.K.T. reports consulting fees from Novartis, Merck, Avalo Therapeutics and Alexion, unrelated to this work.

A.A. has received personal fees from UpToDate (royalty), SOBI (lecture fees), Cadilla Pharmaceuticals (lecture fees), Limbic (consulting) unrelated to this work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2025.152669.

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