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TITLE PAGE

Title: The OMERACT-OARSI core domain set for measurement in clinical trials of hip and/or knee osteoarthritis.

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ABSTRACT

Objectives: To update the 1997 OMERACT-OARSI Core Domain Set for clinical trials in hip and/or knee osteoarthritis (OA).

Methods: An initial review of the COMET database of core outcome sets (COS) was undertaken to identify all domains reported in previous COS including individuals with hip and/or knee OA. These were presented during five patient and health professionals/researcher meetings in three continents (Europe, Australasia, North America). A three-round international Delphi survey was then undertaken among patients, healthcare professionals, researchers and industry representatives to gain consensus on key domains to be included in a core domain set for hip and/or knee OA. Findings were presented and discussed in small groups at OMERACT2018 where consensus was obtained in the final plenary.

Results: Four previous COS were identified. Using these, and the stakeholder meetings, 50 potential domains formed the Delphi survey. 426 individuals from 25 different countries contributed to the Delphi exercise. OMERACT2018 delegates (N=129) voted on candidate domains. Six domains gained agreement as mandatory to be measured and reported in all hip and/or knee OA clinical trials: 'pain', 'physical function', 'quality of life' and 'patient global assessment of the target joint' in addition to the mandated core domain of 'adverse events including mortality'. 'Joint structure' was agreed as mandatory in specific circumstances, stating the specific circumstances, i.e. depending on the intervention.

Conclusions: The updated core domain set for hip and/or knee OA has been agreed upon. Work will commence to determine which outcome measurement instrument should be recommended to cover each core domain.

Keywords: Osteoarthritis; Hip Joint; Knee Joint; OMERACT; Outcome Measure; Clinical Trials

Word Count: Abstract: 250; Main Paper: 2973

INTRODUCTION

Osteoarthritis (OA) is one of the most common musculoskeletal diseases, with an estimated prevalence of 12% to 22% worldwide.(1) It is the leading cause of disability amongst older adults, with an estimated lifetime risk of knee OA being approximately 40% in men and 47% in females.(2) The most common symptoms associated with OA are pain, stiffness and fatigue, associated with disability and loss of physical activity and functional independence.(1,2)

Clinical trials seek to determine whether treatments are safe and beneficial for patients by comparing their relative effects on outcomes chosen to identify benefit or harm.(3) The results can then be used to make decisions on whether a treatment under-investigation should be recommended or not. It is therefore essential that outcomes reported in trials are those which are needed by decision-makers, and reflect meaningful measures for patients, clinicians and other stakeholders.(4,5)

The OMERACT group was established in 1992 with the aim of bringing together people interested in the development, reporting and application of core outcome sets (COS). A COS is an agreed set of outcomes (domains) which clinical trialists should measure and report in all clinical trials of a specific condition.(6,7) A COS also includes recommendations on what outcome measurement instrument should be used to measure these core domains.(6,7) Thus, a COS consists of 'domains' and 'instruments'.

There are four core areas that should be covered in an OMERACT core domain set with at least one domain in each of the areas: death, life impact, and pathophysiological manifestations; and one strongly recommended: resource use (if resource use will not be included, there needs to be an adequate and agreed upon justification for its exclusion).(6) All COS should also consider factors which are not the primary object of research but that may influence the results or the interpretation of the results.(6) These are known as contextual factors.(6) An instrument is the outcome measurement instrument which is recommended to measure that specific domain, e.g. questionnaires to assess quality of life, scales to assess cost, instruments to measure of body function and tests and imaging to assess biomarkers. The key principles for selecting core domains and corresponding instruments are international consultation between patients, health professionals, researchers and industry followed by consensus.(6-8) Through this, any consensus achieved by an OMERACT working group is perceived as being informed through key stakeholder opinion, and to have a worldwide perspective.

In 1997 OMERACT in conjunction with the Osteoarthritis Research Society International (OARSI) developed a COS hip and knee OA,(9) comprising four core domains to be measured and reported in all hip and knee OA clinical trials: pain; physical function; patient global assessment; and for studies with a follow-up period of a year or longer, joint imaging (such as x-ray). Over the past 20 years, there have been developments in how the OMERACT COS are developed, with greater emphasis on patient involvement.(6,10,11) Furthermore, there have been developments in how domains are identified through the recent adoption of the OMERACT Filter 2.0.(6) These guidelines were not established when Bellamy et al(9) developed their COS for hip/knee OA in 1997.

Given developments in methodology, the OMERACT group agreed that the previous hip and knee OA COS should be reviewed. The purpose of this work was therefore to undertake this. To do this, this project was divided into three phases: review of current COS for patients with hip and knee OA (phase 1); Delphi exercise to establish worldwide perspectives on what are potential domains of interest (phase 2); and OMERACT2018 meeting to establish consensus and the update core domain set (phase 3).

This paper reports these phases and presents the OMERACT-OARSI core domain set to measure in clinical trials for people with hip and/or knee OA.

METHODS AND RESULTS

Research ethics approval was gained from the University of East Anglia's (United Kingdom) Faculty of Medicine and Health Sciences Research Ethics Committee on 14th September 2017 (Ref: 2016/2017-104).

Phase 1

All COS that included the views of people with hip or knee OA were reviewed from the COMET (Core Outcome Measures in Effectiveness Trials) database, a repository of published and ongoing COS projects.(12) From 218 COS in musculoskeletal diseases, four COS where identified which included the views of people with hip or knee OA.(8,13-15)

Five patient and health professional/researcher meetings were held to pilot the list of candidate domains, based on the results of the review of the COMET COS, prior to the Delphi project. These

were conducted across three countries (Canada (Toronto), Australia (Sydney) and the UK (Leeds and Norwich)) involving 35 people with hip and/or knee OA, 34 healthcare professionals and one non-clinical researcher. The role of these groups was to determine whether any candidate domains were missing, whether some domains were repetitious and required merging or whether the Delphi Round 1 survey wording was ambiguous. Amendments were made in accordance with these recommendations before launching the Delphi exercise.

Phase 2

Participants and Sample Size

The study flow is illustrated in **Figure 1**. The target population was people with hip and knee OA, and professionals working in areas of relevance to OA, such as healthcare professionals with an interest in OA (e.g., nurses, occupational therapists, orthopaedic surgeons, physiotherapists, rheumatologists), researchers and people working in the pharmaceutical or device industry (e.g. knee braces and orthoses).

There is no consensus on the optimal sample size for a Delphi study.(16) Therefore recruitment was based on time-scale. Round 1 was opened for six weeks (19th December 2017 to 27th January 2018) using a broad sampling strategy to gain as large a sample as was feasible within the study time-frames.

Distribution and Approach

The Delphi survey was distributed through a number of streams to ensure broad coverage to the target population. These included distributing the survey to members of the Osteoarthritis Research Society International (OARSI) members, UK Arthritis Research UK (ARUK) Osteoarthritis Clinical Study Group, recipients of the ARUK e-bulletin, members of the Spanish Society of Rheumatology (SER), the Italian Rheumatology Society (SIR), the European League Against Rheumatism (EULAR) People With Arthritis/Rheumatism (PARE), patient representatives through the Arthritis Foundation's email circulate, Australian 'myjointpain' group and delegates to the Australian OA Summit. There were no restrictions on who from these groups could contribute. In addition, a social media campaign was designed through Twitter to gain further international representation of patient, clinical, research and industry representations.

A window of six weeks was allotted to recruit all potential respondents for Round 1 of the Delphi exercise. A reminder was sent after three weeks. After the six-week recruitment campaign, the

hyperlink for Round 1 was closed. Round 2 was undertaken from 5th February 2018 to 26th February 2018, whilst Round 3 was completed from 5th March 2018 to 25th March 2018.

Process

The Delphi survey was administered via the online software DelphiManager.(17) The DelphiManager programme was presented in English and Italian for the PARE and the Italian Rheumatology Society.

Participants were asked to judge the importance of 50 potential core domains, generated from Phase 1, by answering the question 'how important are the following items to be assessed in trials with people with hip and knee OA?' As adopted previously,(18) responses were measured where 1-3 represented 'not that important', 4-6 'important', 7-9 'critically important'. There was also an 'unable to score' option. We provided an open question where participants could indicate if there were any further domains which should be assessed but was not in the pre-defined list. Where such a response was reported, this was added to Round 2. Participants were also asked whether certain domains should be merged because of perceived overlap, i.e. pain intensity (overall) versus pain intensity (at rest) or pain intensity (with activity).

In agreement with MacLennan et al(19) approach, domains were excluded in Round 2 if they were rated as 'not that important' (≤3 points) by ≥15% of one or more stakeholder groups *OR* included if they were rated as 'important' (≥4 points) by ≤70% of one or more stakeholder groups. If there was agreement from at least 70% of each stakeholder group for a merger of domains, this was performed and included in Round 2 domains.

The Round 2 and Round 3 surveys followed the same format, asking the same questions as Round 1, adopting the same scoring system and approach to domain reduction and merger. Round 2 and 3 participants were provided with the mean responses for each domain from the previous round, presented by stakeholder group (i.e. patients, healthcare professionals, researchers, industry).

Data Analysis

The analysis determined which domains were considered most important to be assessed in future trials of people with hip and knee OA. For this, descriptive statistics and frequency distributions were used to collectively assess all completed Delphi surveys for each of the three Delphi rounds. The data were presented as frequency distributions and mean values with standard deviations where appropriate. Data were analysed by two groups to inform the OMERACT-OARSI core domain set:

'people with OA' vs 'other stakeholder groups'. Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS Inc, Chicago, Illinois).

Formation of the Core Domain Set

The individual item responses provided from the Delphi survey were reviewed and categorised by members of the Working Group under overarching domains. This respected the recommendations made in Filter 2.1.(7) and OMERACT.(19) Based on these domains, the rules for inclusion of domains were:

- **Mandatory (Core) Domains:** domains which were considered as 'critical' by over 70% of both stakeholder groups (patients *AND* others);
- **Important but Optional Domains:** domains which were considered as 'critical' by over 70% of one stakeholder group (either patients *OR* others) but not both;
- **Research Agenda:** domains which need further research.

Adverse events including mortality/survival were included per default as a core domain as per Filter 2.1.(7)

In response to discussions at OMERACT 2018, the OMERACT Onion was adjusted and approved. The OMERACT onion is a schema which illustrates all three constitutes of core domain set (mandatory (core domains); important but optional domains; research agenda), and identified contextual factors.(6) This adjustment adds another layer to the inner circle of the OMERACT Onion structure to allow specification of certain domains as mandatory in specific circumstances.

Delphi Results

The characteristics of those who participated in each round of the Delphi survey are presented in **Table 1**. In total 343 participants completed Round 1 of the Delphi survey, with 177 (52%) and 119 (35%) completing Rounds 2 and 3 respectively (**Figure 1**). **Table 1** illustrates that a cross-section of respondents were represented across the four stakeholder groups, from different continents, representing different clinical presentations or health professionals/research backgrounds.

Table 2 presents the results of the Round 3 Delphi exercise presented by domains by 'people with OA' vs 'other stakeholders' groups. This illustrates those domains and items which reached the *a priori*

threshold for the core domains and for those which were eligible as 'important but optional' and 'research agenda' domains. These results are summarised in **Figure 2**.

Phase 3

The methods and results of Phase 1 and 2 were presented to delegates on Thursday 17th May 2018 at the OMERACT2018 plenary meeting in Terrigal, Australia. This meeting included clinicians, patients and patient representatives, researchers, industry representatives and methodologists. After being presented with this background, delegates were allocated to eight groups where they were asked to consider for 60 minutes the composition of the OMERACT core domain set based on the Delphi Round 3 results as presented in **Table 2**. Each of the eight groups provided feedback after-which 102 delegates voted on the mandatory and important but optional domains. There was 100% agreement that pain, physical function and over 90% agreement that quality of life and patient global assessment of target joint should be included as core domains. However the groups made the following recommendations: moving joint structure into a separate category of 'mandatory in specific circumstances' as there was concern that this would not be relevant for *all* types of osteoarthritis trial interventions (i.e., non-structure modifiable interventions). The variability in Delphi score between patient and other stakeholder votes for a number of domains classified as important but optional (i.e. cognitive function and fatigue) was highlighted by the groups (**Table 2**), and the terminology used to describe activity and participation and direct costs.

Following this, the Working Group members revised the preliminary OMERACT core domain set from the initial vote. A new rule was introduced to account for the wide variability in scores between the 'patient' and 'other stakeholders' groups. Where there was a discrepancy of greater than 30% between the two groups, and where either group presented with less than 85% agreement that the domain was 'critical' to measure, then that would not be eligible for inclusion as an important but optional domain.

The revised core domain set (**Figure 2**) was presented on Friday 18th May 2018 to the OMERACT2018 plenary delegates for a final vote. This included 129 voting delegates. Since the included Core Domain passed the 70% threshold, the votes counted from the previous day's voting were brought forward. Therefore voting was cast on the composition of the Important but optional and research agenda domains. In trials investigating structure modifying interventions, joint structure should be assessed. The results of the vote on the core domain set are presented in **Table 3**. There was agreement by over the 70% threshold required by OMERACT to endorse the core domain set.

DISCUSSION

This paper reports the agreed core domain set, developed using the OMERACT process, with international collaboration across a broad spectrum of key stakeholders involved in the care of people with hip and/or knee OA. This update has overcome previous limitations from the 1997 COS,(9) most notably: greater patient representation, internationalisation of pre-meeting views through an international Delphi, and structuring the findings in accordance to the OMERACT Filter 2.1.(7)

Whilst the domains of pain, physical function and patient global assessment remain core domains, quality of life has been introduced through this updated core domain set. It is likely that further work through OMERACT will be needed to define domains encompassed within the broader concept of 'quality of life'. The project findings also include a number of new domains which are recommended (but not core) for clinical trials and which were not included in the 1997 core domain set.(9) These include: cognitive function, fatigue, sleep, impact of family/caregivers and psychosocial impact. This difference may correspond to the wider contribution of stakeholder views compared to Bellamy et al's(9) COS, particularly the patient perspective. Nonetheless, it represents a change in domain selection towards a more diverse, biopsychosocial evaluation of clinical outcomes.

This is the first OMERACT core domain set to include a contextual factor. The inclusion of adherence was considered important given the results of the Delphi survey where both patient and non-patient groups reported this as critical to include in trials with people for hip and knee OA. The Working Group considered this as a contextual factor as opposed to a domain as it is important to understand how adherent a participant is to an intervention, but it is, in most cases, not necessarily an outcome in itself (unless the trial is designed specifically to assess adherence). Through this means, adherence may be considered useful in the process evaluation of an interventional trial. The Working Group will consider how to expand on this list of contextual factors and determine the composition of this list. We hope the work of the OMERACT Contextual Factors Working Group will assist and guide the concepts and methodologies on how to determine what should be included in this list, to provide a consistent approach in identification and reporting.

This study had a number of limitations. Firstly, as per OMERACT processes, the delegates at OMERACT2018 had the final consensus vote on the core domain set composition. Whilst this included 129 individuals, the percentage of patients in the OMERACT delegate group was smaller than the percentage of patients in the Delphi study. However since delegates based their votes on the findings

from the Delphi survey, this approach was considered appropriate as any voting was therefore underpinned by the views of a wider and more diverse cohort. Secondly, members of the Working Group were required to formulate domains from items reported in the Delphi. Participants in the Delphi survey were required to vote on items rather than domains to provide more detailed views on specific aspects of domains e.g. 'pain intensity' rather than just 'pain'. However this may be viewed as introducing subjectivity in domain formulation. To negate this, the Working Group consisted of a wide variety of stakeholders including clinicians, researchers, methodologists and patients, to ensure that this process followed required OMERACT procedures and research or clinical perspective. Thirdly, both Phase 1 and Phase 2 included representation largely from three continents i.e. Europe, Australasia, North America. There was limited representation from Africa and central Asia. Whilst the social media strategy facilitated recruitment of some participants, most notably from Asia, the results from this core domain set may not necessarily represent global views. This is a recurrent limitation in COS development and one which requires further methodological consideration in future projects. Finally, whilst the Delphi survey gained arrange of responses internationally and from a number of different stakeholders, originally from 343 participants, the final Delphi round consisted of 119 participants and therefore the Delphi only reflected the beliefs of those respondents rather than the 343.

The goal of the next 24 months will be to commence work on assessing instrument selection for mandatory domains from this agreed core domain set. These will be reviewed in accordance with Filter 2.1(7) with the ultimate aim of developing a new core outcome measurement set. In combination with this, the Working Group will promote the dissemination of the core domain set and subsequent COS through presentation of work to patients, healthcare professionals, researchers, regulatory authorities, funders and all individuals and groups involved in the care of people with OA.

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Figure 1: Delphi Study Flow Diagram

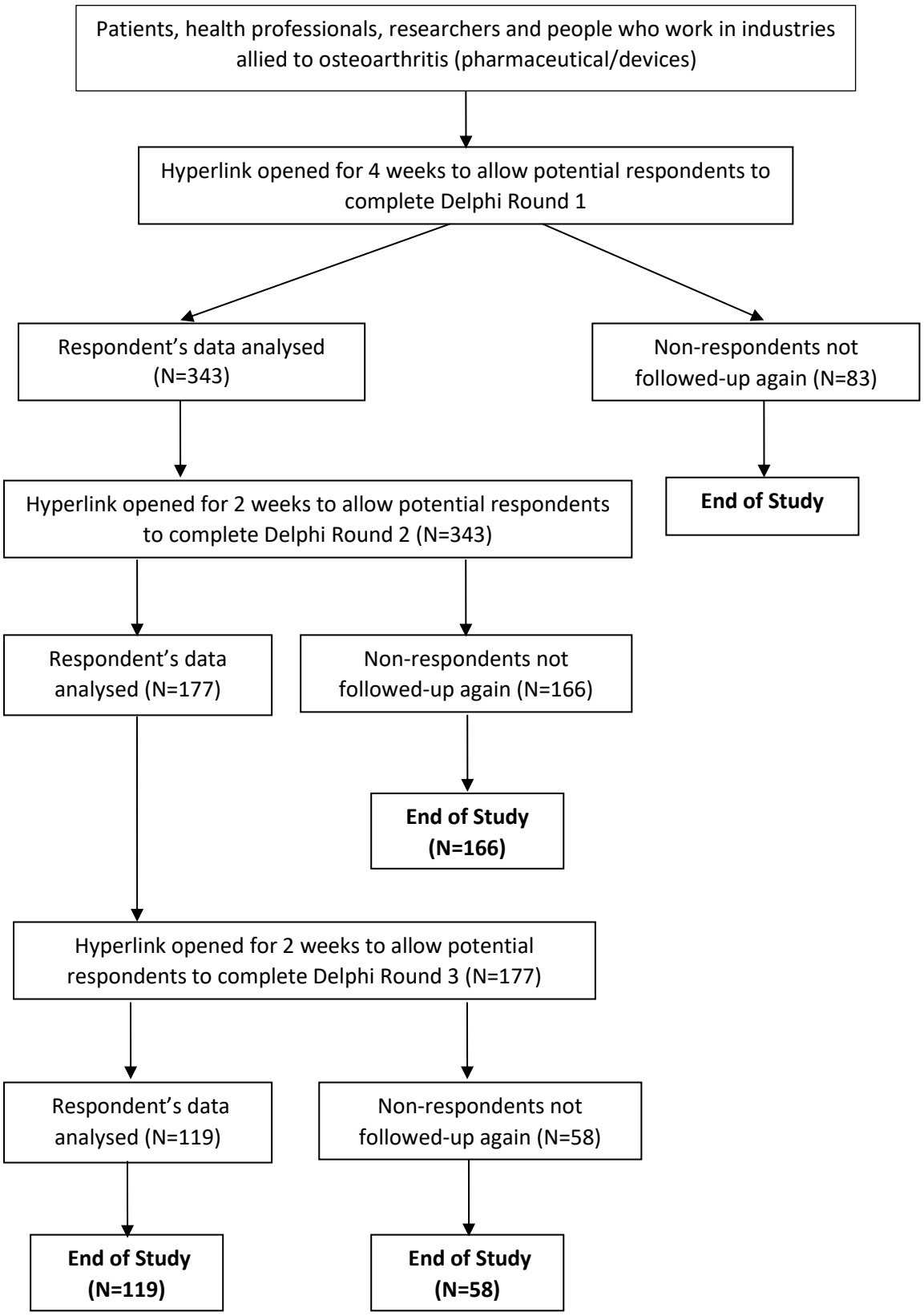

Figure 2: Endorsed OMERACT-OARSI core domain set for trials of people with hip and knee osteoarthritis.

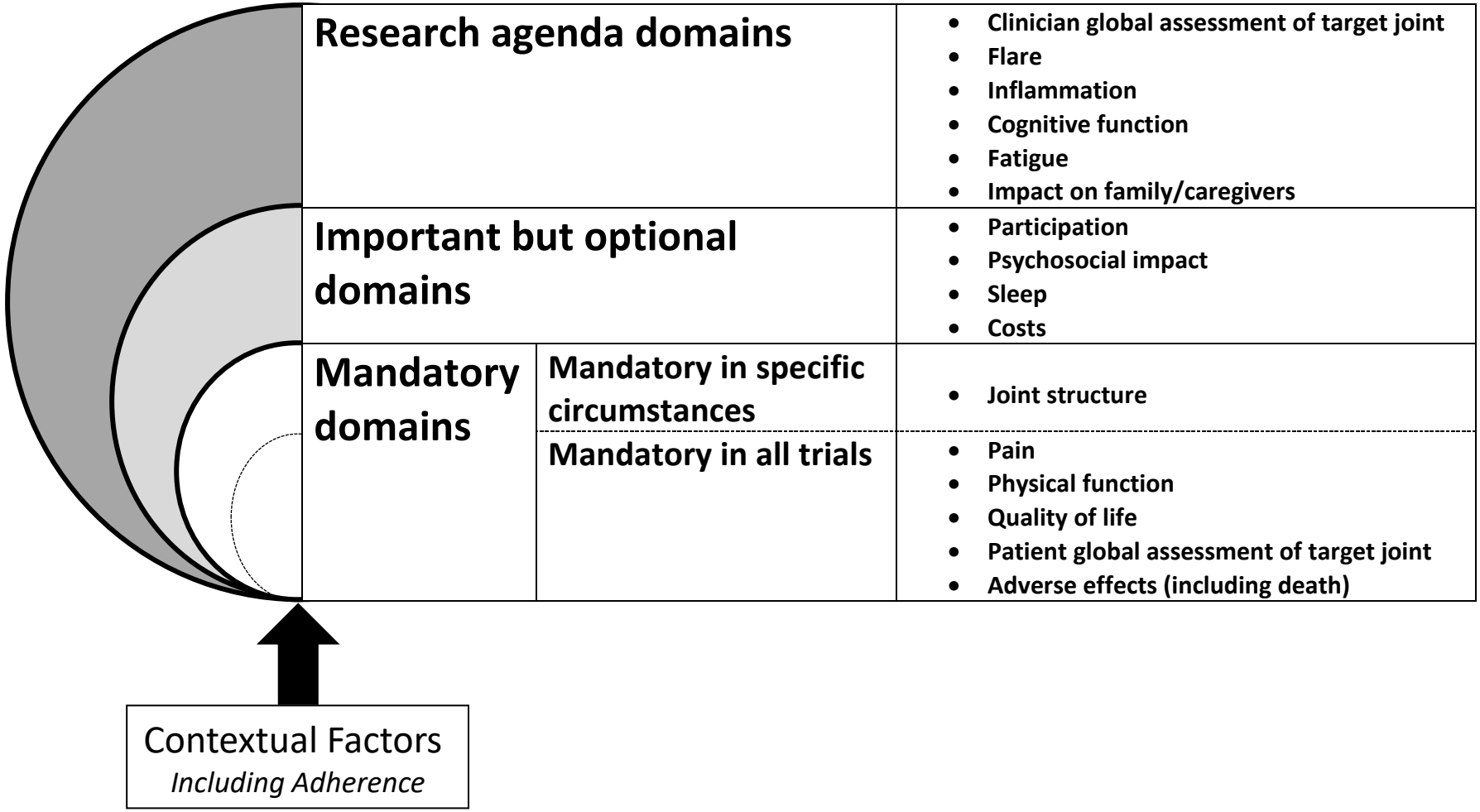

Table 1: Demographic characteristics of Delphi participants

	Round 1 (N; %)	Round 2 (N; %)	Round 3 (N; %)
N	426	177	119
Missing Data	83 (19.5)	0 (0.0)	0 (0.0)
Stakeholders			
Patients with OA	217 (50.9)	67 (37.9)	42 (35.3)
Health Professionals	65 (15.3)	39 (22.0)	29 (24.4)
Researchers	131 (30.8)	65 (36.7)	42 (35.3)
Industry	13 (3.0)	6 (3.4)	6 (5.0)
Gender			
Male	133 (38.8)	65 (36.7)	46 (38.7)
Female	210 (61.2)	112 (63.3)	73 (61.3)
Joint affected by OA			
Knee	78 (22.7)	37 (20.9)	22 (18.5)
Hip	24 (7.0)	15 (8.5)	10 (8.4)
Hip and Knee	73 (21.3)	36 (20.3)	25 (21.0)
Not declared	42 (12.2)	0 (0.0)	0 (0.0)
Not affected by OA	126 (36.7)	89 (22.3)	62 (52.1)
Health Professional Background			
Physiotherapist	61 (36.9)	36 (38.7)	27 (41.5)
Rheumatologist	42 (27.3)	29 (31.2)	21 (32.3)
Health Professional not listed	19 (12.3)	9 (9.7)	5 (7.7)
Clinical Biomedical Scientist	6 (3.9)	3 (3.2)	3 (4.6)
Orthopaedic Surgeon	8 (5.2)	3 (3.2)	2 (3.1)
GP	6 (3.9)	3 (3.2)	1 (1.5)
Occupational Therapist	3 (1.9)	2 (2.2)	0 (0.0)
Holistic Therapist	1 (0.6)	0 (0.0)	0 (0.0)
Clinical psychologist	2 (1.3)	2 (2.2)	1 (1.5)
Nurse	4 (2.6)	4 (4.3)	3 (4.6)
Chiropractor	2 (1.3)	2 (2.2)	2 (3.1)
Country of Response			
Total number of countries represented	25	20	17
UK	126 (36.7)	60 (33.9)	35 (29.4)
Canada	38 (11.1)	21 (11.9)	14 (11.8)
USA	36 (10.5)	17 (9.6)	13 (10.9)
Australia	91 (22.8)	48 (27.1)	36 (30.3)
Spain	6 (1.5)	3 (1.7)	2 (1.7)
Switzerland	1 (0.3)	0 (0.0)	0 (0.0)
Denmark	7 (1.8)	5 (2.8)	3 (2.5)
The Netherlands	7 (1.8)	5 (2.8)	2 (1.7)
Brazil	1 (0.3)	0 (0.0)	0 (0.0)
Germany	5 (1.3)	2 (1.1)	2 (1.7)
China	1 (0.3)	0 (0.0)	0 (0.0)
New Zealand	1 (0.3)	0 (0.0)	0 (0.0)
Belgium	2 (0.5)	1 (0.3)	1 (0.8)
Iceland	2 (0.5)	1 (0.3)	1 (0.8)
Norway	3 (0.8)	2 (1.1)	1 (0.8)

Japan	1 (0.3)	0 (0.0)	0 (0.0)
Ireland	3 (0.8)	2 (1.1)	0 (0.0)
Israel	1 (0.3)	0 (0.0)	0 (0.0)
Italy	2 (0.5)	1 (0.6)	1 (0.8)
Myanmar	1 (0.3)	1 (0.6)	0 (0.0)
France	2 (0.5)	2 (1.1)	2 (1.7)
India	1 (0.3)	1 (0.6)	1 (0.8)
Sweden	3 (0.8)	3 (1.7)	3 (2.5)
Russia	3 (0.8)	1 (0.6)	1 (0.8)
Singapore	1 (0.3)	1 (0.6)	1 (0.8)

GP – general practitioner; N – number of participants; OA – osteoarthritis; UK – United Kingdom; USA – United States of America

Table 2: Formatted Delphi Round 3 results to illustrate the core areas, domains and items for the Round 3 Delphi results

	Domain	Item	People with OA N=42 (%)	Other Stakeholder Groups N=77 (%)	Weighted average (1:1) (%)	All stakeholders N=119 (%)
MANDATORY						
Death	Death	Mortality/survival	76	72	74	78
Life Impact	Pain	Pain (overall)	98	97	98	97
		Pain with activity	98	97	98	97
		Pain at rest	86	90	88	88
		Pain during the night	95	82	89	88
		Pain during the day	93	79	86	84
	Physical Function	Mobility (such as walking)	100	96	98	98
		Leg function (patient reported)	98	79	89	86
		Personal activities of daily living (e.g. washing; dressing; toileting)	81	86	84	84
		Sports, Exercise and Physical Activity	74	70	72	76
	Quality of Life	Quality of life	98	94	96	96
		Overall impact of OA on the person with OA (patient reported)	93	90	92	91
	Patient Global Assessment of Target Joint	Overall improvement of the disease (patient reported)	81	82	82	82
	Adherence	Adherence to a treatment or therapy	93	79	86	85
Pathophysiological Manifestations	Joint Structure	Imaging (such as x-ray; MRI; ultrasound) reflecting changes in joint structure	71	40	56	63
IMPORTANT BUT OPTIONAL						

Life Impact	Activity and Participation	Role function (ability to do work or vocational activities)	79	68	74	71
	Psychosocial Impact	Control over disease (self-efficacy including understanding of the condition)	83	61	72	69
		Perceived ability to cope with their OA (patient reported)	83	59	71	67
		Social withdrawal and isolation	79	43	61	55
	Sleep	Sleep (including falling and staying asleep)	88	57	73	68
	Physical Function	Joint control e.g. giving way (patient reported)	95	34	65	56
		Balance	90	25	58	49
		Muscle strength	86	47	67	62
		Joint range of motion	81	29	55	48
		Exercise tolerance and endurance	71	30	51	45
	Flare	Flares of OA	71	47	59	56
	Patient perception of care	Patient perception of clinician understanding of OA	95	28	62	55
	Clinician Assessment of OA Impact	Overall impact of OA on the person with OA (clinician reported)	76	23	50	42
	Cognitive Function	Cognitive or mental functioning	71	20	46	38
Pathophysiological Manifestations	Biomarkers	Inflammation	74	31	53	46
		Abnormal central nerve changes	71	14	43	34
Resource Use	Direct Costs	Healthcare utilisation (including costs and pain killer use; hospital admission and consultation with clinicians)	79	66	73	75
		Time to surgery (such as joint replacement)	83	42	63	61

RESEARCH AGENDA						
	Clinician Global Assessment of Target Joint	Overall improvement of the disease (clinician reported)	67	21	44	37
	Fatigue	Fatigue	67	23	45	38
	Impact on family, care givers	Impact of disease on family; carers and friends	52	11	32	25
	Cosmetic	The appearance of the leg (e.g. leg shape and cosmetic appearance of lower limb)	14	4	9	8

OA - osteoarthritis

Table 3: Summary of the voting scores for the core domain set from OMERACT2018.

Domain	Voting for Inclusion %
Mandatory	
Pain	100
Physical Function	100
Quality of Life	90
Patient Global Assessment of Target Joint	91
Joint Structure	80
Important But Optional Domains	
Participation	95
Psychosocial Impact	71
Sleep	81
Costs	77
Research Agenda	
Clinician Global Assessment of Target Joint	82*
Flare	
Inflammation	
Cognitive Function	
Fatigue	
Impact on Family/Caregiver	

***** A vote was made for the Outer Circle collectively