

# Developing consensus on core outcome sets of domains for acute, the transition from acute to chronic, recurrent/episodic, and chronic pain: results of the INTEGRATE-pain Delphi process



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## Summary

**Background** Pain is the leading cause of disability worldwide among adults and effective treatment options remain elusive. Data harmonization efforts, such as through core outcome sets (COS), could improve care by highlighting cross-cutting pain mechanisms and treatments. Existing pain-related COS often focus on specific conditions, which can hamper data harmonization across various pain states.

**Methods** Our objective was to develop four overarching COS of domains/subdomains (i.e., *what* to measure) that transcend pain conditions within different pain categories. We hosted a meeting to assess the need for these four COS in pain research and clinical practice. Potential COS domains/subdomains were identified via a systematic literature review (SLR), meeting attendees, and Delphi participants. We conducted an online, three step Delphi process to reach a consensus on domains to be included in the four final COS. Survey respondents were identified from the SLR and pain-related social networks, including multidisciplinary health care professionals, researchers, and people with lived experience (PWLE) of pain. Advisory boards consisting of COS experts and PWLE provided advice throughout the process.

**Findings** Domains in final COS were generally related to aspects of pain, quality of life, and physical function/activity limitations, with some differences among pain categories. This effort was the first to generate four separate, overarching COS to encourage international data harmonization within and across different pain categories.

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**Interpretation** The adoption of the COS in research and clinical practice will facilitate comparisons and data integration around the world and across pain studies to optimize resources, expedite therapeutic discovery, and improve pain care.

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**Keywords:** Core outcome sets; Delphi method; Acute pain; Transition from acute to chronic pain; Recurrent/episodic pain; Chronic pain

### Research in context

#### Evidence before this study

Core outcome sets (COS) have been developed for many health and pain-related conditions, but COS capturing shared experiences across pain conditions do not yet exist for the field of pain. We conducted a literature review to identify all articles that developed, updated, or implemented a COS for pain conditions or health conditions where pain is a major symptom in adults. Published articles were identified from PubMed (including Medline) and from the COMET database, and results of the literature review were used to inform the present Delphi study, which aimed to develop COS for: acute pain, acute to chronic pain, recurrent/episodic pain, and chronic pain.

#### Added value of this study

This study demonstrates consensus on pain domains for four overarching core outcome sets of acute, acute to chronic,

recurrent/episodic, and chronic pain. These COS were developed with expert stakeholders across a range of disciplines, countries, and backgrounds, and uniquely included equal participation of people with lived experience (PWLE). The results of the study support outcome measures that are holistic in nature, covering biological, psychological, and social aspects of the pain experience.

#### Implications of all the available evidence

Clinicians and researchers should consider measuring these outcomes to holistically understand their patient's experiences with pain and gain an understanding of treatment outcomes. Further, the COS can facilitate data harmonization in research and clinical settings, which can spark improvements in scientific and clinical knowledge, which could improve future treatment approaches.

## Introduction

Pain is the leading cause of disability worldwide, and negatively impacts individuals' well-being and carries significant financial burden.<sup>1</sup> The United Nations and international medical societies view access to effective pain management as a fundamental right. Yet, pain is grossly undertreated,<sup>2</sup> causing public health challenges and ethical problems. Like the causes of pain themselves, reasons for its undertreatment are multifactorial. One contributing factor is the lack of rigorous tools to synthesize data across research and clinical practice, especially data encompassing the biopsychosocial nature of pain. Core outcome sets (COS) hold promise for improving data synthesis and subsequently identifying clinically meaningful, biopsychosocial treatment outcome measures.

COS of domains provide researchers with standardized outcome domains that should be assessed and reported in all clinical trials, studies and practices, in specific areas of health or health care.<sup>3</sup> COS

development entails a consensus process, which first identifies *what* to measure (i.e., domains/subdomains) and then identifies *how* they should be measured (i.e., patient-reported outcome measures; PROMs).<sup>3</sup> COS can be used with additional outcome domains and offer the potential to boost rigor and generalizability by improving data harmonization across studies, facilitating meta-analyses, improving systematic reviews, reducing risks of bias in reporting, and using stakeholder consensus to increase the likelihood that measured outcomes are meaningful.<sup>3-6</sup> Numerous COS have been developed for specific pain conditions.<sup>7-9</sup> However, pain categories (i.e., acute, transition from acute to chronic, episodic/recurrent, and chronic),<sup>2,10</sup> which can differ in their biopsychosocial mechanisms and treatment approaches, are often not captured separately.

Although previous initiatives represent important efforts toward data harmonization within diagnostic areas, the heterogeneity across existing COS makes it

difficult to compare treatment effects across pain conditions. This limits progress in several ways. First, chronic pain is increasingly understood as a stand-alone health condition with shared biopsychosocial mechanisms across separate diagnoses.<sup>10</sup> Separating findings based on diagnosis risks missing the discovery of cross-cutting treatments that could broadly reduce the burden of pain. Second, the rate of chronic overlapping pain conditions (COPC) is high,<sup>11</sup> so that the existing condition-specific COS might not fully capture the pain experience for a substantial proportion of individuals with COPC. Third, besides the considerable number of existing COS recommendations for chronic pain,<sup>12</sup> other pain categories (e.g., acute pain) are underrepresented in COS development. Finally, existing COS for pain have variably engaged stakeholders<sup>13</sup> – specifically people with lived experience (PWLE) of pain – and have inconsistently used a biopsychosocial perspective.<sup>14</sup>

To address these limitations, the Innovative Medicines Initiative (IMI)-National Institutes of Health (NIH) Transatlantic Emphasis Group on Research and Translation-to-care Efforts for Pain (INTEGRATE-Pain) Consortium<sup>15</sup> aimed to develop COS of domains for pain. The specific objective and scope of this initiative was to develop consensus on stakeholder-driven COS across pain conditions within four categories (acute, transition from acute to chronic, recurrent/episodic, and chronic pain) for use with adults in clinical research and practice. Stakeholders included people with lived experience of pain (PWLE), researchers, clinicians, and other stakeholders (e.g., regulators, governmental agencies, payers) to best capture biopsychosocial dimensions of pain in the COS. The present COS initiative was unique in that we aimed to develop separate COS based on pain categories across the spectrum for acute to chronic pain. Given the unique experiences, mechanisms, and treatments needed to address each of the categories, we hypothesized that the resulting domains/subdomains for each pain category would be uniquely different.

## Methods

An overview of the methods used in the present initiative is provided below. The [Supplemental Materials](#) contain detailed information about each step. Importantly, PWLE's perspectives were integrated across procedures. The study began in December 2020 and ended in January 2023.

### Protocol and registry entry

The protocol was developed according to COMET Handbook recommendations<sup>3</sup> and guidance from two advisory committees (ACs) (researchers and PWLE). The proposed COS was registered in the COMET database (<https://www.comet-initiative.org/Studies/Details/2083>) and is reported here according to COS-STAR standards.<sup>16</sup>

### Study design and participants

The development of the COS included PWLE, researchers with pain research and/or COS experience, pain clinicians (e.g., physicians, psychologists, nurses, physiotherapists), pain health technology assessment (HTA) experts, representatives of related organizations, and national health policy staff from participating countries. These stakeholders were experienced in COS development, pain management, and/or the four defined categories on the pain continuum, and they represented many nationalities, largely from North America, Europe, and Oceania (due to the geographic makeup of existing COS studies and PWLE networks and advocacy groups). Stakeholders served on one of the initiative's ACs, attended and contributed to the virtual consensus meeting, and/or voted in the Delphi surveys. Respondents who voted in the Delphi process were identified through the SLR and snowball sampling. Researchers and PWLE who attended the pain domain meeting were asked to recruit respondents for the Delphi study, but PWLE were offered the opportunity to recruit more individuals from their networks to ensure equal representation among researcher/clinician perspectives and PWLE perspectives. See [Supplemental Material](#) (S1.1 and S1.2) for more information.

### Ethics

An NIH Institutional Review Board (IRB) determined this initiative's activities did not qualify as research requiring protections for human participants (see 45 CFR 46 §46.104 subpart D5) and was exempt from IRB approval. Thus, informed consent was not required nor obtained. In compliance with the EU's General Data Protection Regulation, a data protection statement was shown to all voters, which indicated the plan for data storage, usage, and protection.

### Procedures

Four separate COS were proposed for conditions within acute, transition from acute to chronic, recurrent/episodic, and chronic pain. These pain categories and their definitions were further informed by the International Association for the Study of Pain<sup>17</sup> (<https://www.iasp-pain.org/resources/terminology/>), previous public health research,<sup>10,14</sup> and the Acute to Chronic Pain Signatures Program,<sup>18</sup> in combination with feedback from the initiative's advisory committees. [Table 1](#) includes the definitions for the four pain categories.

Members of the steering committee conducted a systematic literature review (SLR) (see S1.3) to generate the initial list of outcome domains/subdomains for the four pain categories prior to the virtual consensus meeting. The ACs, stakeholders at the consensus meeting, and participants in the first round of the Delphi were able to recommend additional domains/subdomains. The Steering Committee, with the assistance of the AC, evaluated these proposed domains/

Pain category	Definition	Example condition(s)
Acute pain	Pain experiences and conditions lasting for a relatively limited time, up to a few weeks, and generally remitting when the underlying pathology resolves; often occurs after trauma, surgical interventions, and some disease processes	Acute post-operative pain, pain in labor, fracture, and ulcer
Transition from acute to chronic pain	Pain experiences and conditions lasting from a few weeks to three months	Post-operative recovery
Recurrent/episodic pain	Pain experiences and conditions lasting for a relatively short time but recurring across an extended period	Sickle cell-associated pain, migraine, polymyalgia rheumatica, calcium phosphate deposition, and dysmenorrhea
Chronic pain	Pain experiences and conditions lasting longer than three months	Chronic low back pain, chronic postsurgical pain, chronic pelvic pain, and diabetic neuropathy

**Table 1:** Pain categories, and their associated definitions and examples, used in the present initiative.

subdomains to identify those that were similar and could be combined.

A consensus process was organized based on COMET Handbook guidelines<sup>3</sup> (Fig. 1).

A virtual consensus meeting (June 2022) was held to discuss COS and vote on whether overarching COS should be created. A three-round Delphi method<sup>19</sup> was subsequently performed between July 2022 and January 2023 with four separate Delphi surveys (one for each pain category) running in parallel. We chose a Delphi process as our consensus method for developing these COS due to its precedent in COS research.<sup>14</sup> For this Delphi process, respondents were provided with lists of outcome domains (with definitions and citations) to rate over three rounds. Three rounds were chosen to offer respondents the opportunity to reflect on the groups' responses each round and to reduce concerns that retention and respondent burden might be greater with more rounds. Domains/subdomains were presented together across rounds (rather than holding distinct rounds to vote on domains or subdomains separately) to limit the number of rounds.<sup>3</sup> The decision to have respondents rate outcomes at the domain and subdomain level (rather than broader areas or specific measures) was also made to give respondents flexibility in prioritizing the level of specificity they felt most relevant to assessment, but not be too broad or too narrow for inclusion into a widely used COS. Fig. 2 shows the overall flow across the three rounds as well as the consensus definition.

Invited individuals were asked to respond in each of the three rounds, regardless of their participation in previous rounds. Surveys were administered with a web-based survey platform (SurveyMonkey, Advantage version, San Matteo, California). Prior to proceeding with domain ratings, respondents were required to watch a short educational video related to COS, Delphi methods, and the purpose and implications of this specific Delphi, and then correctly answer four comprehension questions (unlimited number of attempts).

For the first round, respondents rated all domains/subdomains from the initial list generated through the

literature review, recommendations from the steering and advisory committees, and suggestions from attendees at the preliminary pain domain meeting. Definitions for domains/subdomains were taken or adapted from the literature and included citations. Respondents then rated or ranked domains/subdomains as instructed.

For subsequent rounds, respondents were asked to reflect on their own responses and the overall group responses. To facilitate this, we provided respondents with the previous round's ratings (broken down by stakeholder group), answers to frequently asked questions or comments, and the opportunity to receive a copy of their personal responses emailed to them upon request.

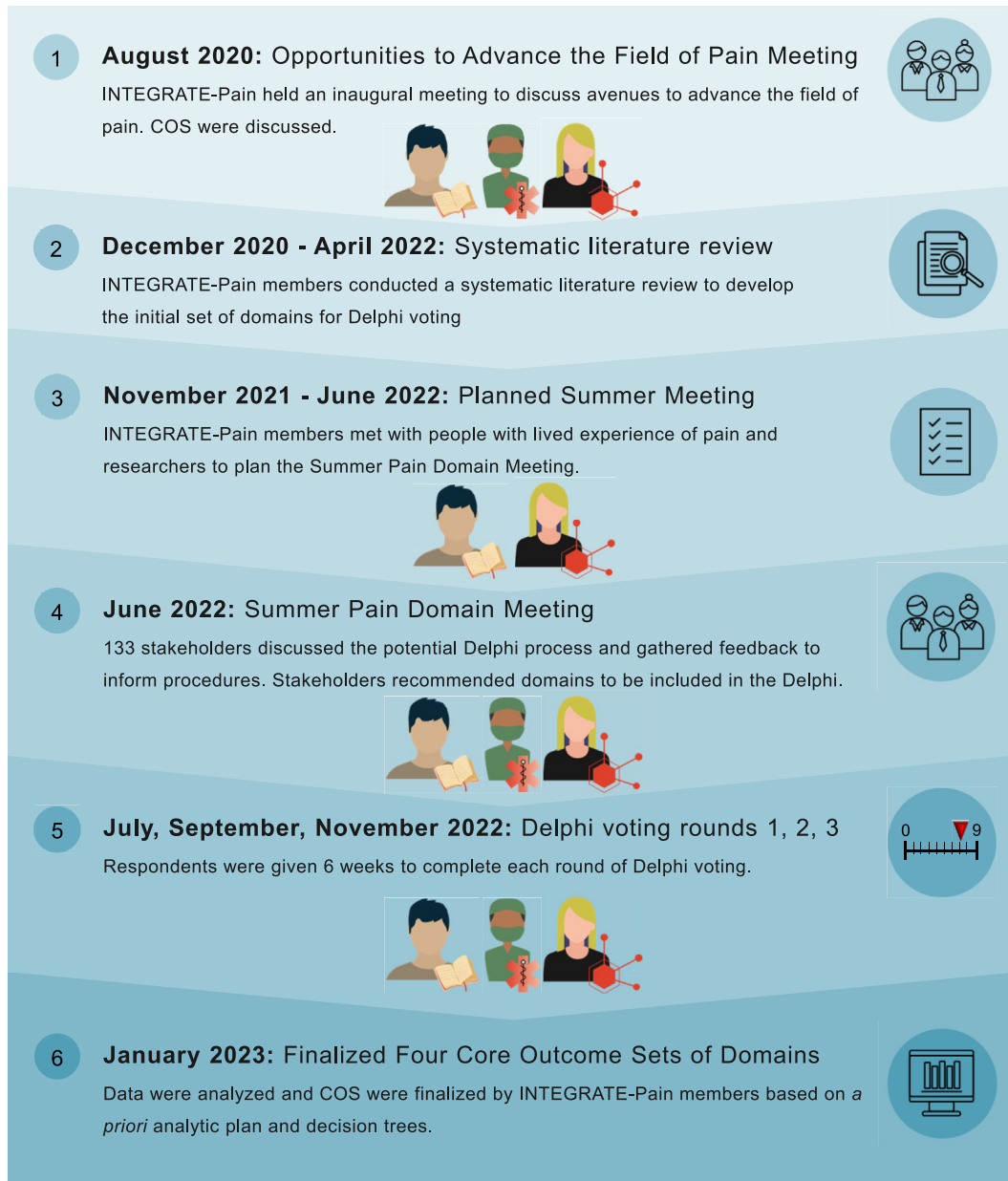
Criteria for including a domain/subdomain in the subsequent round or final COS were determined and communicated to the respondents prior to the beginning of each Delphi round.

**Data analysis**

In rounds 1 and 2, respondents rated each domain/subdomain according to its importance for inclusion in the respective pain category's COS. Domains/subdomains were rated using a 9-point Likert scale from the GRADE handbook (<http://wwwcc-imsnet/gradepr>) based on previous recommendations<sup>19,20</sup>: 1–3 = “not important,” 4–6 = “important, but not critical,” or 7–9 = “critical”. An additional option was 0 = “unable to rate”. In round 1, respondents could also recommend domains/subdomains that were not included to potentially advance to round 2. This was not an option after round 1 because we wanted respondents to have an opportunity to recommend domains, but needed to eliminate domains as we progressed each round. There is also precedent in COS research for allowing domain suggestions only during the first round.<sup>8</sup>

In round 3, respondents rank ordered all domains/subdomains that advanced from round 2 based on their importance for the respective pain category's COS. Flexibility in rating approach, such as switching from rating to rank ordering domains/subdomains, has been previously used to reduce respondent burden and facilitate consensus.<sup>21</sup>

## INTEGRATE-Pain Core Outcomes Sets (COS) Project Timeline

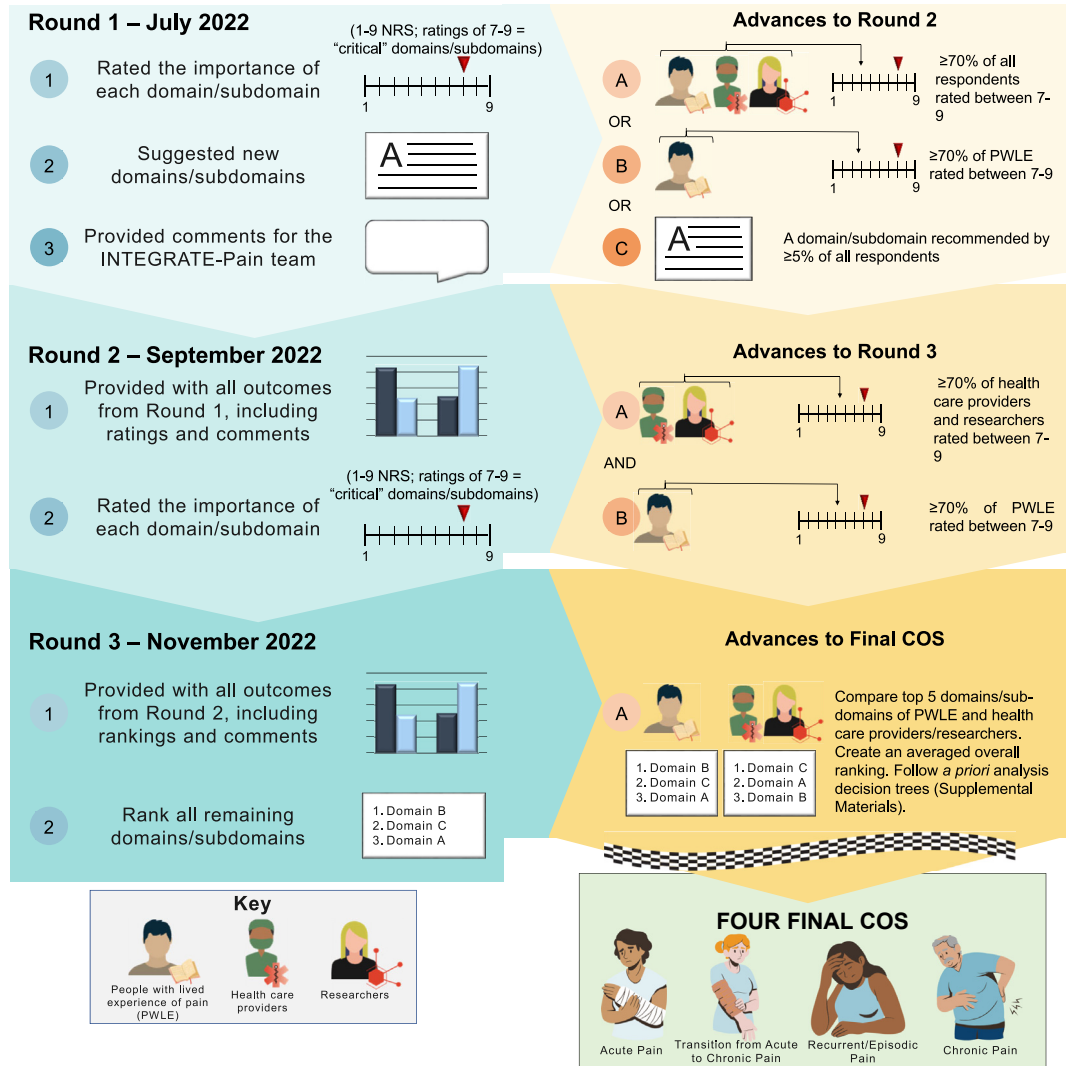


### Stakeholders Engaged During The Step



Fig. 1: The timeline for the INTEGRATE-Pain core outcomes set initiative.

## Delphi Voting Process for All Four COS



**Fig. 2:** Methods and consensus definition decisions involved in the Delphi method across all three rounds. Based on advice from the advisory committees and feedback from Delphi respondents, changes in procedures were made (as advised) and clearly communicated to Delphi respondents prior to the dissemination of the subsequent round.

Analytic plans and criteria to advance domains/subdomains and reach consensus were determined a priori and communicated to the respondents before each Delphi round (Fig. 2). Analyses were conducted and are reported separately for each of the four COS. Within a given COS, responses were divided into two groups: [1] PWLE and [2] researchers (R), clinicians (C), and others (O) or R/C/O. This approach served to weigh PWLE's responses equally with R/C/O, even if less than 50% of the respondents were PWLE in each round.

In round 1, domains/subdomains moved forward to round 2 if either [1]  $\geq 70\%$  of PWLE rated the domain/subdomain between 7 and 9 (i.e., "critical"), or [2]  $\geq 70\%$

of the entire group (i.e., PWLE + R/C/O combined) rated the domain/subdomain between 7 and 9. These thresholds were adapted from previous COS development and recommendations outlined by Williamson and colleagues.<sup>13</sup> Our thresholds were slightly modified from the literature to simplify criteria for advancing domains since initial lists were comprehensive and we sought to eliminate domains each round. We also sought to ensure voices of PWLE were heard.<sup>13</sup> We received consultation and guidance from members of our advisory committee (experienced in COS research and Delphi methods) on how to appropriately adapt the recommended guidelines for our study's specific aims

and needs. New domains/subdomains were added to round 2 if  $\geq 5\%$  of respondents suggested it in round 1. This liberal threshold was set to encourage respondent input without advancing items suggested by only one respondent.

In round 2, domains/subdomains moved forward to round 3 if  $\geq 70\%$  of PWLE and  $\geq 70\%$  of R/C/O rated the domain/subdomain between 7 and 9. This stricter threshold was set to narrow the number of domains/subdomains to those that both groups found meaningful.

In round 3, the average rank orders of domains/subdomains were calculated separately for PWLE and R/C/O. The top five for each respondent group were retained. The items were then ordered based on their average ranking across both groups. For example, a domain/subdomain ranked highest in one group (ranking = 1) and fourth highest in the other group (ranking = 4) would have an averaged rank value of 2.5. The domains were then ordered according to these averaged rank values. The top five items were included in the final COS. [Figure S3](#) shows the a priori decision tree analysis for final consensus. The final COS was restricted to the top five domains/subdomains to not be overburdensome to patients, researchers and clinicians. Domains/subdomains ranked within one group's top five that did not rank highly enough for the final COS are listed as items to be considered. We met with our advisory committees between each Delphi round. At the end of the Delphi, we met with the multidisciplinary group of PWLE and researchers on our advisory and steering committees to discuss and finalize the COS. We also communicated to respondents our plan to disseminate the results via webinars, conferences, and email communication.

### Role of the funding source

Funders of the IMI-PainCare initiative (the NIH did not receive any funding) had no role in study design, data collection, data analyses, data interpretation, or writing of report.

## Results

The main outcomes are reported below. The [Supplemental Materials](#) provide additional results.

### Protocol deviations

The study team proposed a protocol that indicated how the team would move a domain/subdomain forward after each Delphi round. This information was disseminated to the respondents at the start of the Delphi. The AC recommended modifying the protocol before the start of ratings in round 2 and before the start of round 3 ranking to address issues related to overlapping/similar domains and ensure equity in respondent representation. The Delphi respondents were

notified of the change in protocol prior to the beginning of each round. Please refer to [Supplemental Material S1.4.](#) and [Figure S3](#) for more information.

### Delphi respondents

In total, 446 unique individuals were identified as candidate respondents for the four pain groups. However, because some individuals were asked to vote in more than one pain category, a total of 627 survey invitations were sent. Of the invited individuals, 357 participated in at least one Delphi round. [Table 2](#) shows respondents' sociodemographic characteristics based on stakeholder group (PWLE or R/C/O) and pain COS category. [Table 3](#) shows the response rates by pain group, which ranged from 74% for chronic pain to 81% for recurrent pain. Of the stakeholders invited to participate in the Delphi, 89 did not participate in any of the surveys, 45% of which were PWLE and 55% of which were R/C/O. Refer to the supplement for more details about respondents.

### Outcomes

All domains/subdomains presented to respondents during each round are displayed in the [Supplemental Materials](#). Refer to [Table S6](#) for respondent dropout rates.

There were  $n = 27$  domains/subdomains considered in round 1 for acute pain. Of those,  $n = 9$  advanced to round 2, and  $n = 8$  were added because of respondent recommendations. For round 2,  $n = 17$  total domains/subdomains were presented. Of those,  $n = 7$  advanced to round 3.

There were  $n = 16$  domains/subdomains considered in round 1 for transition from acute to chronic pain. Of those,  $n = 9$  advanced to round 2, and  $n = 9$  were added because of respondent recommendations. For round 2,  $n = 18$  total domains/subdomains were presented. Of those,  $n = 7$  advanced to round 3.

There were  $n = 24$  domains/subdomains considered in round 1 for recurrent/episodic pain. Of those,  $n = 11$  advanced to round 2, and  $n = 8$  were added because of respondent recommendations. Two of the domains that advanced (pain frequency and pain recurrence) were folded into a recommended domain (pain temporality) that consolidated several similar/overlapping domains. For round 2,  $n = 17$  total domains/subdomains were presented to respondents, of which  $n = 8$  advanced to round 3.

There were  $n = 65$  domains/subdomains considered in round 1 for chronic pain. Of those,  $n = 29$  advanced to round 2, and  $n = 1$  was added because of respondent recommendations. Two domains from round 1 (pain frequency and pain duration) were consolidated into another similar/overlapping domain (pain temporality) that had advanced. In round 2,  $n = 28$  total domains/subdomains were presented to respondents, of which  $n = 12$  advanced to round 3.

	Acute pain			Transition from acute to chronic pain			Recurrent pain			Chronic pain		
	Overall (n = 69)	R/C/O (n = 36)	PWLE (n = 33)	Overall (n = 88)	R/C/O (n = 40)	PWLE (n = 48)	Overall (n = 72)	R/C/O (n = 22)	PWLE (n = 50)	Overall (n = 254)	R/C/O (n = 156)	PWLE (n = 98)
<b>Gender</b>												
Female	41	16	25	52	20	32	54	13	41	162	87	75
Male	27	20	7	33	19	14	15	9	6	83	63	20
Reported as Unknown	0	0	0	0	0	0	0	0	0	1	1	0
Other	1	0	1	0	0	0	3	0	3	4	2	2
<b>Sex assigned at birth</b>												
Female	40	16	24	51	19	32	50	12	38	151	84	67
Male	26	19	7	29	17	12	14	8	6	74	56	18
Intersex	0	0	0	0	0	0	0	0	0	0	0	0
Reported as Unknown	0	0	0	0	0	0	0	0	0	1	1	0
<b>Member of minority group</b>												
Identify as	26	12	14	35	10	25	34	5	29	76	31	45
R/C/O	31	31	0	25	25	0	15	14	1	127	125	2
PWLE	30	0	30	39	1	38	39	0	39	80	1	79
Both	7	5	2	22	12	10	15	7	8	41	26	15
<b>Years of clinical experience</b>												
<1	1	1	0	0	0	0	0	0	0	0	0	0
1-5	2	2	0	3	2	1	1	1	0	12	8	4
6-10	3	2	1	4	3	1	5	2	3	16	13	3
>10	30	28	2	29	24	5	22	18	4	129	116	13
<b>Years of research experience</b>												
<1	1	0	1	1	0	1	3	0	3	7	4	3
1-5	12	5	7	12	3	9	14	4	10	27	16	11
6-10	7	5	2	7	6	1	3	1	2	36	24	12
>10	31	25	6	36	29	7	21	15	6	117	101	16
<b>Years of COS experience</b>												
None	8	4	4	21	2	19	23	2	21	39	11	28
<1	10	2	8	17	3	14	12	0	12	33	11	22
1-5	21	12	9	19	12	7	10	4	6	50	31	19
6-10	8	4	4	11	7	4	8	3	5	38	30	8
>10	22	14	8	20	16	4	19	13	6	94	73	21
<b>Region of residence</b>												
North America	33	14	19	58	28	30	44	11	33	127	71	56
Europe	25	15	10	14	4	10	16	7	9	78	45	33
Oceania	6	3	3	10	6	4	6	2	4	26	19	7
Middle East	0	0	0	2	1	1	1	1	0	7	6	1
Africa	1	0	1	0	0	0	4	0	4	0	0	0
Asia	1	1	0	0	0	0	0	0	0	2	2	0
South America	1	1	0	0	0	0	0	0	0	3	3	0

Total counts may be less than actual n because voters were not required to answer all demographic questions.

**Table 2: Self-reported demographics and classifications for voters in the Delphi surveys, including researchers, clinicians, and others (R/C/O) and people with lived experience of pain (PWLE).**



	Acute pain	Transition from acute to chronic pain	Recurrent pain	Chronic pain	Total
Invited to Vote, n	86	108	89	344	627
Total in pain group who voted, n (%)	69 (80%)	88 (81%)	72 (81%)	254 (74%)	483 (77%)
R/C/O who voted, n (% of total voters)	42 (49%)	47 (44%)	26 (29%)	201 (58%)	316 (50%)
PWLE who voted, n (% of total voters)	44 (51%)	61 (56%)	63 (71%)	143 (42%)	311 (50%)

The number of respondents for each group represents those who participated in at least one round of the Delphi. Some individuals were invited to vote in multiple groups due to having experience with multiple pain categories, therefore the totals have duplicate votes since some individuals voted in multiple categories.

Table 3: Response rates for Delphi by pain category.

### Final Core Outcome Sets (COS) Based on Delphi Voting

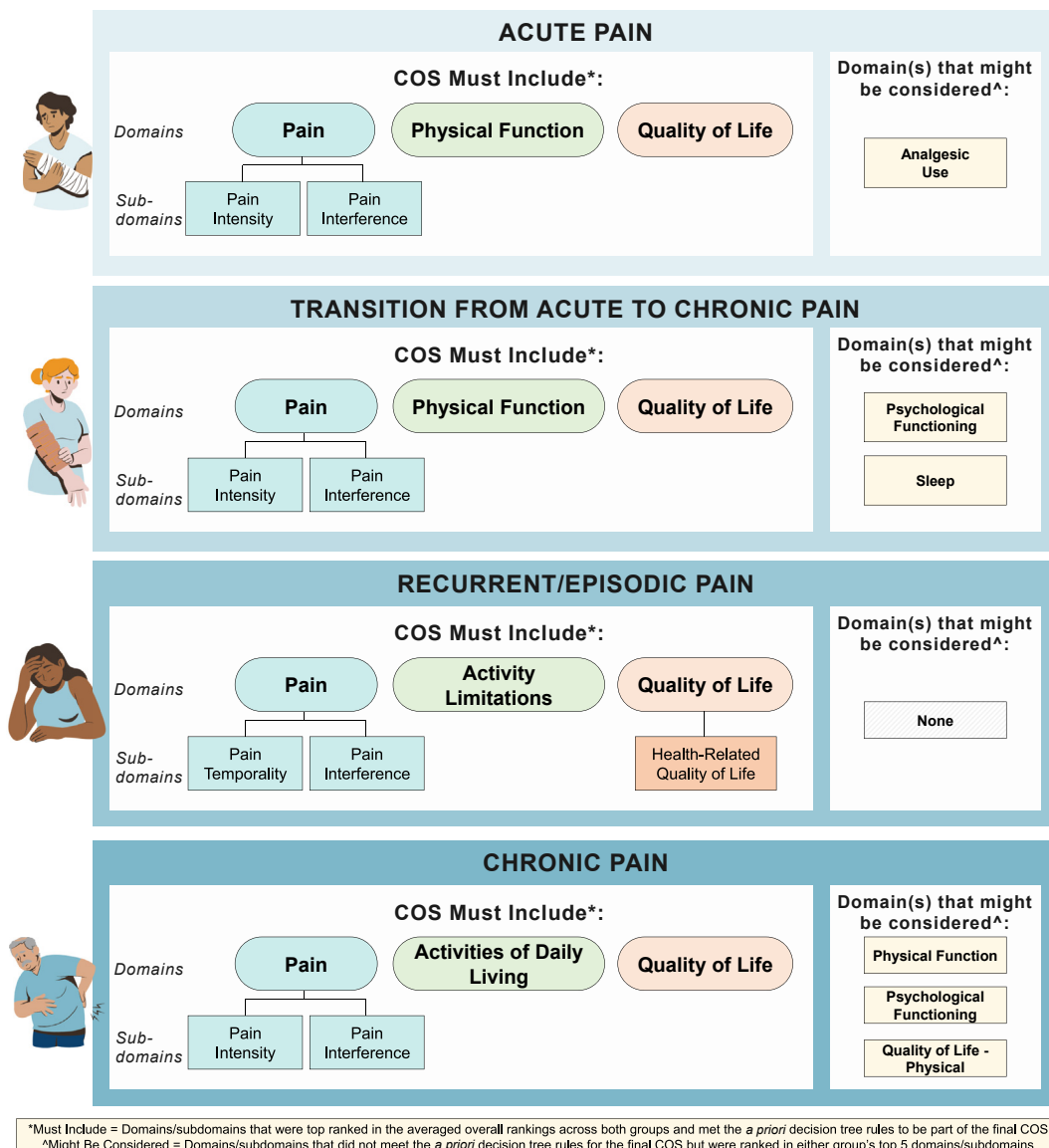


Fig. 3: Final core outcome sets across all four pain stage categories.

**Core outcome sets**

Fig. 3 shows the final domains included in the acute, transition from acute to chronic, recurrent/episodic, and chronic pain COS, and Table 4 provides their definitions and final results for their transition from round 2 to round 3 for all four pain categories.

The final COS for acute pain included pain (which must include measures of pain intensity and pain interference as subdomains), physical function, and quality of life (as a broad construct). Although not part of the final COS, investigators also might consider measuring analgesic use since it was among domains included in at least one group’s top five ranking.

The final COS for transition from acute to chronic pain included pain (which must include measures of pain intensity and pain interference as subdomains), physical function, and quality of life. Although not part

of the final COS, investigators might also consider measuring psychological functioning and sleep since they were among domains included in at least one group’s top five ranking.

The final COS for recurrent/episodic pain included pain (which must include measures of pain interference and pain temporality as subdomains), quality of life (which should include a measure of the subdomain health-related quality of life), and activity limitations.

The final COS for chronic pain included pain (which must include measures of pain intensity and pain interference as subdomains), quality of life, and activities of daily living. Although not part of the final COS, investigators might also consider measuring physical function, psychological functioning, and physical quality of life since they were among domains included in at least one group’s top five ranking.

Domain	Definition	Included in final COS for			
		Acute pain	Transition from acute to chronic pain	Recurrent pain	Chronic pain
Pain	An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.	Yes	Yes	Yes	Yes
Pain Intensity	Magnitude of the pain sensations experienced (in the past week).	Yes	Yes	N/A	Yes
Pain Interference	The degree to which there are consequences of pain on aspects of a participant’s life (in the past 24 h or past week for acute or chronic pain, respectively).	Yes	Yes	Yes	Yes
Quality of Life	Broad multidimensional concept that usually includes subjective evaluations of both positive and negative aspects of life.	Yes	Yes	Yes	Yes
Physical Function	Ability to carry out activities requiring physical actions.	Yes	Yes	No	Consider
Sleep	Perceptions of difficulty falling asleep, sleep quality, sleep depth, duration and restoration associated with sleep.	No	Consider	No	No
Analgesic Use	Use of a drug that reduces pain.	Consider	N/A	N/A	Dropped
Psychological Functioning	The ability to achieve one’s own goals within themselves and the external environment. It includes an individual’s behavior, emotion, social skills, and overall mental health.	Dropped	Consider	Consider	Consider
Activities of daily living	Fundamental skills required to independently care for oneself, such as eating, bathing, and mobility.	Dropped	Dropped	Dropped	Yes
Quality of life (physical)	Subjective evaluations of both positive and negative aspects of physical life (i.e., pain and discomfort, energy and fatigue, sexual activity, sleep and rest, sensory functions).	N/A	N/A	N/A	Consider
Health Related Quality of Life	At an individual level, HRQOL includes physical and mental health perceptions (e.g., energy level, mood) and their correlates—including health risks and conditions, functional status, social support, and socioeconomic status.	N/A	N/A	Yes	No
Disability	Any condition of the body or mind (impairment) that makes it more difficult for the person with the condition to do certain activities (activity limitation) and interact with the world around them (participation restrictions).	N/A	N/A	Dropped	No
Pain Affect	The distress caused by the pain, reflecting the emotional response to pain.	N/A	N/A	N/A	No
Medication Use	Use of correct (and/or incorrect) medication.	Dropped	N/A	No	N/A
Pain Temporality	Variability in intensity, time to onset of meaningful pain relief, durability of pain relief, and frequency, duration and intensity of episodes of breakthrough pain.	N/A	Dropped	Yes	Dropped
Activity Limitations	A dimension of disability, such as difficulty seeing, hearing, walking, or problem solving.	Dropped	N/A	Yes	Dropped

Yes = Included in final COS; Consider = Not included in final COS but could be considered based final voting results; No = Voted out in final round of Delphi Survey; Dropped = domain was voted out in an earlier round of Delphi survey for that pain condition. N/A = Domain was not voted on for that pain condition.

**Table 4: Final core outcome set (COS) domains/subdomains and their respective definitions.**

## Discussion

Existing pain-related COS focus on specific conditions, hampering cross-cutting integration of data to improve generalizability of research and clinical practice. The INTEGRATE-Pain Consortium aimed to develop overarching COS across pain conditions along the spectrum from acute to chronic pain. Our consortium led a comprehensive consensus process to develop four COS for acute pain, transition from acute to chronic pain, recurrent/episodic pain, and chronic pain. A virtual consensus meeting was held to determine whether the pain community believed these four COS were needed. Meeting participants decided it was important to proceed with a three-round Delphi, which was performed from July 2022 to January 2023. At the end, respondents reached consensus on the most important domains/subdomains for inclusion into four COS. We hypothesized that although similar wide-ranging sets of biopsychosocial outcomes would be relevant to conditions within a given pain category, there would be unique domains/subdomains perceived as critical by stakeholders across pain conditions within each category with little overlap across categories. This hypothesis was only partially supported, as there was substantial overlap across the four final COS. All final COS included pain, pain interference, and quality of life as domains/subdomains. Furthermore, all final COS included one domain/subdomain related to activities of daily living/activity limitations/physical function, supporting the multidimensional (biopsychosocial) nature of pain. Although we suggest that these COS be adopted for inclusion in research and clinical practice, they do not preclude the addition of other outcomes as appropriate to specific pain or health conditions.

There are some domains/subdomains, such as physical function (included in the acute and transition from acute to chronic pain categories), activity limitations (recurrent/episodic pain), activities of daily living (chronic pain) and pain interference (all categories), that are similar to each other, but also have unique attributes that can be distinctly measured. For example, physical function is the ability to carry out activities requiring physical actions.<sup>14</sup> Activity limitations is a dimension of disability, such as difficulty seeing, hearing, walking, or problem solving.<sup>22</sup> Pain interference is the degree to which there are consequences of pain on aspects of a participant's life (in the past 24 h or past week for acute or chronic pain, respectively).<sup>23</sup> With respect to the quality of life domain, Delphi respondents were provided with outcomes at different levels of specificity. We included outcomes at the domain and subdomain level to be inclusive for the initial list of domains in round one. For rounds two and three, we sent an FAQ (responses to Frequently Asked Questions/Comments) along with the Delphi survey that asked respondents to consider the level of specificity in their voting choices. Some pain groups (acute, transition, chronic) consented

on the broader domain quality of life, while the recurrent group consented on the subdomain health-related quality of life. These differences are reflected in the final COS, and we recommend researchers and clinicians consider the tension between generalizability and specificity in their application of these COS as appropriate to their research and clinical settings. Example measures for these domains/subdomains are, respectively, Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function scale,<sup>24</sup> the World Health Organization Disability Assessment Schedule 2.0,<sup>25</sup> and the PROMIS Pain Interference scale.<sup>23</sup> However, the “how” to measure the outcomes/subdomains needs further systematic research followed by a final consensus process on the COS of PROMs for each pain category. The result of our Delphi provides COS with lists of domains achieved by respondent consensus. Pain intensity was included in three out of the four COS. However, pain intensity did not reach consensus for the recurrent/episodic pain COS; instead, pain temporality was included by Delphi participants, indicating the importance of frequency and duration of pain.

There are two intended principal uses for the present COS. First, they can be used in research to supplement measures that researchers already collect for certain conditions. In this way, the COS can advance the pain field through data harmonization across studies without limiting innovation within specific projects. Second, these four COS can be used as a minimum set of measures in clinical practice with the goals of applying a more holistic framework in clinical decision-making, benchmarking, and addressing common limitations in clinical practice.<sup>26</sup> The COS are not meant for diagnostic purposes; rather, the outcomes should be measured in research and clinical practice where the diagnosis of the health or pain condition has already been determined. Finally, they are not intended to be used as the only measures. Therefore, our COS are limited to five domains because burden on patients should be carefully considered when choosing the number and length of measures included in a COS.<sup>26</sup>

Our approach had several strengths. The domains/subdomains in our COS were agreed upon by a broad range of respondents, including PWLE, respondents from many countries, and respondents with previous experience in COS research related to pain, including from a wide range of disease backgrounds. As COS should be meaningful and accessible to PWLE, our initiative heavily incorporated their views while addressing challenges faced by COS developers, such as aligning researchers'/clinicians' research efforts to PWLE's concerns, preferences, and respondent burden, securing international input, and achieving consensus among disparate stakeholder groups.<sup>27</sup> Another strength of our approach is that we sought feedback from PWLE advisors throughout the Delphi process. We also

prioritized inviting PWLE to participate in the Delphi surveys and structured our analytic plan to promote equal representation among PWLE and R/C/O. The diversity of views represented in the final COS and the robust inclusion of PWLE could increase their uptake and acceptance.

These strengths are balanced with several limitations. First, because the COS literature is concentrated in North America, Europe, and Oceania, our process of using a SLR to invite stakeholders and participants contributed to limited representation of individuals outside of these regions, and the Delphi was only offered in English. Greater representation from under-represented world regions, as well as minoritized racial/ethnic groups, is critical for promoting health equity in future COS development. The use of snowball sampling (asking stakeholders to identify additional participants from their networks) in recruiting PWLE for participation also hampered diverse representation among PWLE in the study. Despite this limitation, we found snowball sampling helped to facilitate the inclusion of many PWLE to enable equal representation between R/C/O and PWLE, a unique facet of this Delphi. Second, although these COS were designed for clinical research and practice, we recognize that these two applications have different demands and requirements. We tried addressing this concern by including researchers, clinicians, and PWLE as respondents. However, we anticipated that this diverse group of stakeholders would have disparate experiences with and opinions on clinical research and practice, which can impede clarity on what consensus means.<sup>28</sup> Therefore, all respondents completed a short training video with comprehension questions related to COS and the purpose and implications of this Delphi and its resulting COS. Future work is needed to evaluate these COS across settings to determine potential implementation barriers. Third, a barrier across COS development is variable uptake.<sup>29</sup> Previous work has shown that this might be largely due to researchers' preferences to prioritize other outcome measures and limited knowledge about the COS' existence.<sup>30</sup> Fourth, the flexible and complex nature of Delphi studies (which asks for voting over multiple rounds and reflection on group responses) can lead to drop-outs and introduce bias towards majority views.<sup>28</sup> To mitigate turnover, we allowed registered participants to vote in any round, regardless of their participation in previous rounds. To reduce risk of the majority views influencing individual responses, we reiterated the purpose of the study each round, providing clear instructions and responses to frequently asked questions. Lastly, a barrier to uptake is the lack of recommendations regarding *how* to measure the outcomes. To encourage effective and widespread adoption of these COS, INTEGRATE-Pain will engage professional organizations to gather endorsements for the COS and facilitate dissemination. We will emphasize

the use of these COS alongside disease-specific COS. For research where pain is only one symptom of the disease under study, we also will encourage researchers to use these COS. To inform PWLE globally, our PWLE advisors asked to partner with INTEGRATE-Pain to develop materials that will communicate key findings and implications among PWLE.

The present initiative follows recommended guidance for COS development describing that a consensus process should first identify *what* to measure and then identify *how* they should be measured.<sup>3</sup> Since the aim of this Delphi was to obtain agreement on *what* to measure, the next step for the field of pain will be to reach consensus on *how* to measure these domains. However, recent research has shown that many PROMs for acute and chronic pain lack validity and reliability among various populations.<sup>14</sup> Therefore, a challenge for future researchers will be to determine how to create or adopt PROMs for the domains in these COS that can be generalized across cultures, languages, backgrounds, and disorders. In the meantime, researchers and clinicians can apply the present COS in their work by using PROMs that measure the consensus-driven domains/subdomains.

The INTEGRATE-Pain Consortium brought together a large and diverse group of stakeholders to develop COS for acute, transition from acute to chronic, recurrent/episodic, and chronic pain. Our final COS have the potential to improve data harmonization and allow for comparisons across pain conditions and intervention approaches. For these implications to be realized, however, the present COS must be effectively incorporated in research and clinical practice. Moving forward, INTEGRATE-Pain will work with stakeholders to disseminate these COS and promote their uptake in the field of pain.

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All authors read and approved the final version of the manuscript.

All authors had access to the deidentified data used in this study and accept responsibility for the decision to submit the manuscript for publication.

Giulia Bova, Andrew Siddons, Laura Wandner, Daniela Rosenberger, Janelle Letzen, Esther Pogatzki-Zahn, and Ulrike Kaiser have directly accessed and verified the underlying data reported in the manuscript.

#### Data sharing statement

Individual participant data that was collected throughout the research process from Delphi participants is not available to others. De-identified participant data was aggregated for analysis and presented in an anonymized format through tables in the article and supplement. All other research data is unavailable.

#### Declaration of interests

Giulia Bova has nothing to disclose.

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#### Appendix A. Supplementary data

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