Title: Developing a Core Outcome-domain Set to assessing Effectiveness of Interdisciplinary Multimodal Pain Therapy - The VAPAIN consensus statement on core outcome-domains

Running head: Multimodal Pain Therapy for chronic pain

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Abstract

Interdisciplinary multimodal pain therapy (IMPT) is a biopsychosocial treatment approach for patients with chronic pain that comprises at least psychological and physiotherapeutic interventions. Core Outcome Sets (COSs) are currently developed in different medical fields to standardize and improve the selection of outcome-domains, and measurement instruments in clinical trials, to make trial results meaningful, to pool trial results, and to allow indirect comparison between interventions. The objective of this study was to develop a COS of patient-relevant outcome-domains for chronic pain in IMPT clinical trials.

An international, multi-professional panel (patient representatives (n=5), physicians specialized in pain medicine (n=5), physiotherapists (n=5), clinical psychologists (n=5), and methodological researchers (n=5)) was recruited for a 3-stage consensus study, which consisted of a mixed-method approach comprising an exploratory systematic review, a preparing online survey to identify important outcome-domains, a face-to-face consensus meeting to agree on COS domains, and a second online survey (Delphi) establishing agreement on definitions for the domains included.

The panel agreed on the following eight domains to be included into the COS for IMPT: *pain intensity, pain frequency, physical activity, emotional wellbeing, satisfaction with social roles and activities, productivity* (paid and unpaid, at home and at work, inclusive presentism and absenteeism), *health-related quality of life*, and *patient's perception of treatment goal achievement*.

The complexity of chronic pain in a biopsychosocial context is reflected in the current recommendation, and includes physical, mental and social outcomes. In a subsequent step measurement instruments will be identified via systematic reviews.

Introduction

Interdisciplinary multimodal pain therapy (IMPT) is a biopsychosocial approach for patients with chronic pain[12,13,14,24,26,27,30], meanwhile recognized internationally[15,32]. IMPT consists, minimally, of psychological and physiotherapeutic interventions, aiming to increase patients' physical and psychological function and activity towards defined goals and improving adjustment to pain. In some countries additionally active participation of physicians is mandatory[21]. Existing diversity of outcomes[8], and methodologies for outcome assessment[22], hampers comparison of clinical trials (including outcome-reporting bias[42]), and knowledge translation[8]. The development of a core outcome set (COS) would address this situation[8,42]. A COS is defined as a minimum set of relevant outcome-domains, and reliable measurement instruments within those domains, that are required to be measured and reported in all clinical trials[28].

Developing COSs involves a multi-method approach consisting of systematic reviews and consensus processes[2,34]. The application of COSs should not be restricted to clinical trials only. Its application in routine care supports generation of evidence from observational studies and clinical registries as well[6]. It seems reasonable to create a COS which can be used across all study designs both in efficacy/effectiveness studies, and routine daily record keeping. A COS for daily record keeping refers to standardized documentation, with a minimal amount of outcome-domains, monitoring the patient's status throughout routine care and can be simultaneously used for quality management purposes.

The involvement of key stakeholders is highly recommended by the HOME roadmap (*Harmonizing outcome Measurement in Eczema*) for COS development[34], with methodological approaches such as the use of expert panels, and considered essential for acceptance of a COS by future users[25,31]. For IMPT, relevant stakeholders consist of at least all key health professions involved, patient representatives, physicians specialized in pain medicine, physiotherapists, clinical psychologists, and methodological researchers.

The discussion about COS in the therapy of chronic pain has been established by IMMPACT[17], and developed by other initiatives recently[20]. Nevertheless heterogeneity of outcome assessment is still present[8]. Applying COS in IMPT requires a multidimensional approach, consisting of biological, psychological, and social aspects thus mirroring therapy aims. IMMPACT[37,38], as the most acquainted initiative, defined COS for all forms of chronic pain therapies, but focused mainly on medication in clinical trials[36] and not on comprehensive therapy approaches such as IMPT.

Inclusion of patients in COS development is recommended to provide a patient perspective on relevant outcome-domains[2]. Patient preferred domains[38] do not consistently match with previous COS recommendations[37], and this gap remains to be filled.

Therefore, two main reasons exist to develop a COS in IMPT[19]:

1. IMPT patients have protracted, and ongoing, pain. Pain interferes with most life domains, thus changes in biopsychosocial aspects need to be considered when assessing therapies.

2. The primary aim of IMPT is not reduction of pain in the first instance, but focusing on general improvements in physical, psychological, and social aspects according to patients' experience.

"Validation and Application of a patient-relevant core set of outcome-domains to assess multimodal PAIN therapy" (VAPAIN)[19] targets on developing a consensus-based COS of patient-relevant outcome-domains for chronic pain in IMPT for efficacy/effectiveness studies (ES) and daily record keeping (DRK).

Methods

Protocol, registration and ethical approval

Reporting of this study follows the Core Outcome Set-Standards for Reporting (COS-STAR)[23] guidelines. The study protocol was published *a priori* [19], along with the registration of VAPAIN in the *Core Outcome Measures in Effectiveness Trials* (COMET) database[7]. Ethical approval was obtained from the Ethical Committee of the Medical Faculty of the Technical University Dresden (EK 105032015).

Organization of the VAPAIN consensus process

Three groups with different functions were involved into project conduction: the VAPAIN steering committee (UK, SD, CK, KN, LJ, RS), the VAPAIN advisory board and the VAPAIN panel. The steering committee was responsible for conducting all systematic literature reviews, the planning, conducting and preparing of all results to be provided to the VAPAIN panel for the consensus process on domains and definitions. The steering committee was not involved into content related activities. The VAPAIN advisory board consisted of clinicians, methodological researchers, and patient representatives and was responsible to observe and advice the project realization to ensure high quality. It was independent in person and action from all the other VAPAIN groups. The VAPAIN panel was invited to discuss and vote, to align on outcome domains for IMPT.

Eligibility criteria: Selection of the VAPAIN panel

Eligibility of VAPAIN panel members was defined as being representative of a relevant stakeholder group of IMPT in clinical research and/or daily practice: patients, physicians specialized in pain medicine, physiotherapists, clinical psychologists, and methodological researchers. VAPAIN panel members were experienced in their fields (clinicians were supposed to be at least acquainted with IMPT and its therapeutic components), were nominated by international organizations, and scientific associations related to pain and/or chronic pain to control for selection bias, and were able to take part in the full process.

Project schedule

We conducted a 3-stage consensus study, using a mixed-methods approach (*fig. 1*) consisting of an initial systematic review[8], preparing online survey to identify outcome-domains (initial outcome-domains; *step 1, 1.1-1.2*; April-June 2014), a 2-day face-to-face consensus meeting to discuss and agree on COS domains (November 2014, *step 1, 1.3*), and a further online survey (Delphi) to establish agreement of domain definitions included in the COS (March-October 2015, *step 2, 2.1-2.3*). All stages were supervised by a multi-professional advisory board (including patient representatives) for quality assurance throughout.

Information sources

-Systematic review: First (see *fig. 1*), a systematic review was conducted to prepare a list of the most reported outcome-domains for chronic pain in the context of IMPT[8]. More than 140 different outcome-domains with different abstraction levels and conceptual quality were identified. It was infeasible to provide all of these to the VAPAIN panel for consideration; therefore only outcomes found in at least 10% of included studies were selected. Thus, a total of 19 outcome-domains were included (*table 1*). The Patient-Reported Outcomes Measurement Information System (*PROMIS*)[3,16] was assumed the theoretical framework to classify identified outcome-domains, capturing the biopsychosocial model of chronic pain and IMPT. Domains were organized into physical, psychological, and social health areas as aspects of health condition that need to be measured to appropriately assess the effects of a health intervention and comprises domains as components of core areas to be a specification of an aspect of health[2].

- ***online survey domains:*** To prevent selection bias, the VAPAIN panel was asked during *round 1.1* (*fig. 1*) to add relevant outcome-domains not found among the 19 domains pre-selected. The pre-selected domains were provided with definitions according to literature. The outcome-domains indicated by the VAPAIN panel were forwarded into the domain selection without restriction. No other a priori criteria were applied at this point.
- ***face-to-face meeting:*** Prior to the meeting, all VAPAIN panel members received a booklet with pertinent information regarding the development of COS, VAPAIN, and additional publications for information about domains. Presentations provided information about IMPT, COS initiatives, HOME roadmap of COS development, the VAPAIN study, and the results from the online survey.

To avoid intimidation of the patient representatives, several strategies were used to promote their participation. Prior to the meeting patients had been invited to a briefing, at which the organizers explained the rationale of the meeting, definitions, and their role as participants. The small group discussions were held in peer groups so that patients had the opportunity to identify themselves as a group, and discussion in the large group started with the results of the patient peer group. During the large group discussion the facilitator started with patients' opinions, and supported different perspectives when they were presented by patient representatives. If the VAPAIN panel was not able to agree to a construct, patients' perspectives determined the final panel decision.

More details regarding the meeting can be found at VAPAIN Website[38].
- ***online survey domain definitions:*** For all of the consented domains officially published and consented definitions if available were presented to the VAPAIN panel. Supplementary notes from the meeting were provided for a consistent awareness of the previous discussion.

>>Fig. 1

>>Table 1

Consensus process

-Online Survey "domains for ES and DRK" (step 1, round 1.1-1.2)-

The aim of the first online survey (*round 1.1-1.2*) was to prepare preliminary multi-professional and international agreement on a specific COS domains for efficacy/effectiveness studies, and daily record keeping in IMPT.

Participants' characteristics of the VAPAIN panel were obtained.

The initial systematic-review-derived outcome-domains were provided to the VAPAIN panel during ***round 1 of online survey (1.1)*** via ***Delphi manager*** software (supported by the COMET initiative, http://www.comet-initiative.org/delphimanager/). VAPAIN panel members were asked to rate the importance of proposed domains regarding a) efficacy/effectiveness studies and b) daily record keeping. Furthermore, all members specified minimum and maximum number of outcome-domains to be included into the COS for both trial and daily use.

During ***round 2 (1.2),*** VAPAIN panel members received feedback on their own ratings as well as those from the entire VAPAIN panel in a separate document attached to the invitation email. In different colors their personal and the vote of the group were highlighted for each question. New outcome-domains added by VAPAIN panel members in *round 1* were included into *round 2* for rating by all VAPAIN panel members. Participants were informed about the minimum and maximum number of domains (median of positive voting) to be included in the COS, according to results from *round 1*. VAPAIN panel members then indicated outcome-domains to be included in each COS according to the minimum/maximum number stated.

Outcome scoring: The importance of outcome-domains was rated on a scale from 1 to 9, with 1-3 *"not important"*, 4-6 *"important but not critical"*, and 7-9 *"critical"* [18]. VAPAIN panel members were allowed to choose *"unable to score"*. The median was used to summarize results for each domain.

-Presence meeting "domains for ES and DRK" (step 2, 1.3)-

The aim of the meeting was to achieve final consensus of outcome-domains to be included in the COS. A 2-day consensus meeting was held in Dresden, Germany from November 27 to 28, 2014. Two facilitators (EN and UK) guided discussions following group discussion methods[18,43].

The meeting focused primarily on the COS domains for efficacy/effectiveness studies. Participants were separated into stakeholder groups, each supported by one methodological expert. The groups were advised to rate candidate domains as *"included"*, *"unclear"*, or *"excluded"* if considered not important for the COS. Results were presented to the complete panel. Starting patient-centered with the results from the patients' group, all domains labeled *"to be included"* were discussed by the entire group, followed by the *"unclear"* domains.

Panel members were advised to discuss the reasons for inclusion or exclusion of initial domains. They were encouraged to either drop or combine domains or get more abstract levels to feel as secure as possible about comprehensiveness of the domain for patients with chronic pain. The final consensus of the panel, by majority, was required in order to include the specific domain into the COS.

Voting was anonymous and analyzed simultaneously by VAPAIN steering committee members to enable immediate feedback for the discussion. The VAPAIN panel decided to vote anonymously and weighting was therefore not considered necessary by the entire group and steering committee.

Definition of consensus: The panel decided to use ≥70% of VAPAIN panel members voting yes for a domain, to include a domain into the COS[2]. In cases where the 70% criterion was not achieved, domains were discussed again and another vote was taken.

After the COS domains for efficacy/effectiveness studies were agreed, potential outcome-domains for the COS daily record keeping were discussed.

-Online Survey "definition of domains" (step 2, round 2.1-2.3)-

The aim of this online survey was to achieve final consensus on definition of recommended outcome-domains, which was felt to be essential for subsequent systematic reviews to identify the most relevant measurement instruments[19]. The iterative web-based survey consisted of three Delphi rounds, and an intermediate round was conducted via Surveymonkey[35] inviting the same VAPAIN panel members. They were asked to comment on, and rate, the proposed definitions in three rounds (*2.1-2.3*). For *emotional wellbeing* (conceptual divergences within panel members) and *patient's perception of treatment goal achievement* (divergences of wording) an additional round was needed (*fig. 1 step 2, 2.2-1)*.

Outcome scoring: Panel members were asked to rate according to 4 possible categories: *"I agree"*, *"The proposed definition needs modification"*, *"I disagree"*, or *"unable to score"*. For each domain frequencies were estimated for all specific categories.

Definition of consensus: The same rule as described above (*step 2*, face-to-face meeting).

Debating and voting

Discussion was led by two facilitators (EN, UK), aiming that everyone's comment and opinion was heard and sufficiently acknowledged by the entire VAPAIN panel. The facilitators encouraged maximum integration of outcomes of group work (applying nominal group technique), with visual records displayed to aid the process. Starting with the outcome of the patient representatives'

discussion, each domain was discussed in detail by the entire panel, proceeding to a vote once participants felt that all issues related to the particular domain had been comprehensively discussed, and facilitators assured that all panel members felt heard and their views acknowledged. In the case of an ambiguous decision, patient representatives were asked for their views.

Results

Protocol deviations

During the online survey *step 1* it became obvious that the different professions with different backgrounds needed more space for detailed deliberation to enable a final agreement of COS domains by the entire VAPAIN panel. Therefore the last round of *step 1* online survey was skipped and the VAPAIN panel members were invited to the face-to-face-meeting originally planned to decide about measurement instruments. After completing agreement on outcome-domains a Delphi approach was conducted for defining the recommended domains (*fig.1 step 2, 2.1-2.3*) in a supplemental, originally not planned step.

VAPAIN panel members

A total of 25 individuals were recruited (5 of each patient representatives, physicians, physiotherapists, clinical psychologists, and methodological researchers) and addressed as representatives of their organizations (*table 2*). Characteristics are presented in *table 3*. With reference to experience of scientific processes among patient representatives, four out of five were either long-term leading or active members in self-help organizations, had organized meetings, or had collaborated in scientific committees before.

>> Table 2

>>Table 3

Outcomes

Online Survey "domains for ES and DRK" (step 1)

Response rates for *round 1* and *round 2* were 100% (n=25) and 88% (n=22), respectively. VAPAIN panel members decided that the COS domains for efficacy/effectiveness studies should contain a minimum of 4 (in order to be comprehensive enough), and a maximum of 9 domains (due to concern about respondent burden). For daily record keeping a minimum of 3 and a maximum of 6 domains were considered appropriate. In total, 38 outcome-domains were provided and grouped into the 6 core areas of *general quality of life*, *health related quality of life*, *sickness impact*, *mental health*, *social health* and, *physical health*.

A wide range of ratings was observed during both rounds for most of the domains, with a median of ≥7 (see *table 1*) for efficacy/effectiveness studies as well as daily record keeping, indicating very different perspectives among the VAPAIN panel members on what should be measured.

Presence meeting „domains for ES and DRK"(step 2)

COS for efficacy/effectiveness studies (ES) in IMPT

- Results of the small group voting

In summary, patient representatives rated 14 outcome-domains as relevant for a COS for efficacy/effectiveness studies in IMPT. There were large differences between stakeholder groups, most notable between patient representatives and clinical psychologists; 50% (n=7) of the domains voted by the patients as *"critical"*, were voted for exclusion by the clinical psychologists. This observation mainly referred to psychological issues, which patient representatives felt to be of high importance, whereby clinical psychologists defined most of those domains to be rather process variables of IMPT than outcomes. For *pain intensity* and *pain frequency* there was substantial disagreement due to some VAPAIN panel members arguing that both outcome-domains should not be part of the COS in chronic pain since there is not much change during therapy. The opposite opinion was to include both domains because the treatment approach still targets on pain. The sole agreement throughout all groups was observed for *health-related quality of life*.

- Results from the plenary voting

The following eight domains were voted for inclusion by at least 70% of all meeting VAPAIN panel members to be included for efficacy/effectiveness studies: 1) *pain intensity*, 2) *pain frequency*, 3) *physical activity*, 4) *emotional wellbeing*, 5) *satisfaction with social roles and activities*, 6) *productivity (paid and unpaid, at home and at work, including presentism and absenteeism)*, 7) *health-related quality of life*, 8) and *patient's perception of treatment goal achievement* (see *table* 4). Only *pain intensity, pain frequency,* and *health related quality of life* were adopted from the previous online survey, the other domains emerged from debating preselected and provided domains. A short summary of minutes from the face-to-face meeting is available via online supplement.

By reference to OMERACT recommendations[2], the VAPAIN panel recommended *withdrawal from therapy/side effects* as critical domains.

>>Table 4

COS for daily record keeping (DRK) in IMPT

The VAPAIN panel discussed the importance of daily record keeping COSs, referring particularly to the purposes of a COS for daily records, and different national requirements. No agreement was achieved, and the VAPAIN panel decided to primarily focus on the COS in efficacy/effectiveness studies, adjourning the debate about a COS for daily record keeping.

Online Surveys "definitions of domains" (step 2, 2.1-2.3)

During online survey *round 2.1-2.3* (*fig. 1, table 5*), VAPAIN panel members were provided with possible definitions (*step 2, presence meeting*). For *emotional wellbeing,* VAPAIN panel members received three possible definitions[9,10,40]; the wording of *patient's perception of treatment goal achievement* was discussed at length. Response rate of the four rounds (three to discuss, and vote, for domain definitions and an additional round to clarify the definitions of *emotional wellbeing* and *patient`s perception of treatment goal achievement*) ranged from 100% (*2.1, 2.3*) to 80% (*2.2, 2.2-1*). Final results are presented in *table 5*. For all outcome-domain definitions but one (*pain frequency)* a consensus was achieved.

>> Table 5

Discussion

Following an iterative process of evidence synthesis and international multi-stakeholder discussion among patient representatives, physicians specialized in pain medicine, physiotherapists, clinical psychologists, and methodological researchers, eight core outcome-domains were consented to be used in every efficacy/effectiveness study in interdisciplinary multimodal pain therapy.

All outcome-domains are provided with a definition agreed by the VAPAIN panel, except *pain frequency*. During the face-to-face-discussion, several earlier mooted outcome-domains were subsumed or changed into other outcome-domains. The VAPAIN recommendation comprises three frequently reported (*pain intensity*, *pain frequency* and *health related quality of life*)[8], and five outcomes less commonly used. The balance of physical outcomes (*pain intensity, pain frequency, and physical activity*), psychological outcomes (*emotional wellbeing*), social outcomes (*satisfaction with social roles and social activities*, *productivity*) and overarching outcomes (*health related quality of life*, *patient's perception of treatment goal achievement*) satisfies the requirement for biopsychosocial applicability. There was discussion of the possible need in addition for outcome-domains specific to conditions such as low back pain, headache or neuropathic pain.

A core set for daily record keeping was not achieved due to dis-agreement amongst VAPAIN panel members on the purpose, and aim, in IMPT, further complicated by different national requirements, and resources. Nevertheless the VAPAIN panel did not reject the importance of a COS for daily record keeping.

Since the perspective of IMPT is multidimensional, the interests and perspectives at the beginning of the process were predictably heterogeneous. Legitimate differences of opinion were due to the multidisciplinary, personal and national backgrounds, and only by open face-to-face-discussion was it possible to achieve consensus on outcome-domains, as well as on umbrella terms and handling of subgroup specific views.

The use of consistent outcome-domains in trials would be an important contribution to assist in understanding the common problem of differing results between efficacy and effectiveness studies. Therefore, the uniform inclusion of the VAPAIN COS (including *withdrawal from therapy/side effects)* is recommended for both effectiveness and efficacy studies.

Efficacy/effectiveness cannot be assumed but needs to be proven by relevant (also including patient-relevant) criteria normally defined a priori and derived from the needs of a specific patient population. Treatment approaches can thereby be estimated to be beneficial or not, and compared to other interventions in order to estimate superiority for a specific health condition. Therefore it is necessary to start from therapy aims (as operationalized in outcome parameter and based on patients' needs) to identify effectiveness of interventions. Following this idea, outcome domains need to refer to what is important to patients undergoing the intervention, and need to be multidimensional in the case of chronic pain. The relevance of therapeutic aims in the development of COS has not been adequately discussed to date and this could lead to insufficient coverage of a COS for a specific target population. This might be an important issue particularly in future applications of COS.

VAPAIN has started with therapeutic aims of IMPT, providing the basis for further investigation of which kind of interventions or combination of interventions (including dose, and content) best serve patients with chronic pain. This might lead to future adaptations of the composition of interventions of IMPT, enlighten the superiority of one intervention above others (e.g. specific physiotherapeutic or psychological interventions) by meta-analyses or even result in adaptations of treatment models. The provision of specific designed multicomponent treatments for specific subgroups of patients with chronic pain in public health delivery, including restricted applications of IMPT for patient with lower levels of chronicity, would be a potential and resource-saving consequence.

For the consideration of representativeness and generalizability of the findings, several aspects need to be addressed. The sample size in this project refers to the amount of specialists of IMPT who were willing to participate as well as to financial budget. Even though the eligibility criteria demanded clinicians experienced in the field of IMPT, it was not possible to ensure such an expertise internationally, so it was accepted when experienced clinicians were acquainted to IMPT, and experienced in the field of comprehensive pain therapy, even if their work environment did not

match the applied definition of IMPT completely. Nomination by scientific organizations was addressed to ensure a broad variety of international members, but many of the nominated individuals came from Germany where IMPT is frequently applied. Another limitation is the design of the first step; whereby systematic review identified outcome-domains were pre-structured before providing to VAPAIN panel voting. This was necessary because of the excessive number of identified outcome-domains in effectiveness studies investigating IMPT. The opportunity to add additional outcome-domains was considered valid and important.

Outcomes need to be important to patients, clinicians, and other key decision makers[25,31]. Patient perspective has often been insufficiently considered when developing COSs, or introduced only at a late stage. In VAPAIN, patient representatives were involved from the outset. Their opinions were invited first. The inclusion of patients legitimized the process and influenced the discussion at every point, such as the meaning of psychological factors and their heterogeneous distribution, or the difference between *physical function* and *activity*. Even though the participating patient representatives have been identified by public self-help organizations, the question remains if their opinion reflects the experience of the majority of patients with chronic pain. A potential selection bias could arise from the social background, financial resources and educational level of patients willing to participate in scientific processes. According to previous investigations on patients with chronic pain in a German sample the VAPAIN domains have essentially been validated[27]. Another survey in patients with chronic pain reveals considerable overlaps with the VAPAIN recommendation (*emotional wellbeing*, *physical activities*, several *social* areas), especially emphasizing the social component (8 out of 19 domains)[38].

Compared to other recommendations (e.g. IMMPACT[37,38], on low back pain[5]) VAPAIN has produced some different results. VAPAIN has primarily focused on a specific, per se, heterogeneous sample (chronic pain) for a specific treatment approach (IMPT) in efficacy/effectiveness studies, considering chronic pain as a bio-psycho-social phenomenon, referring to PROMIS framework[3,16] as a relevant framework capturing bio-psycho-social perspectives on health care. The different scopes of other outcome initiatives particularly regarded to drug trials[37], or a specific target population (non-specific low back pain[5]). Both initiatives focus on functional aspects (*physical*), and *pain intensity*[5,37], added by *emotional functioning*, *participants' ratings of global improvement*, *symptoms and side effects* as well as *participants dispositions*[37], or *HrQL* and *number of death*[5]. Domains such as productivity or work ability, important domains according to the public health perspective, and ensuring patients' social participation and financial security, were not considered[37] or excluded[5], while domains concerning social participation have not been recommended. Regarding the psychological health area VAPAIN recommended *emotional wellbeing* instead of *emotional functioning*[37]. Despite the fact, that *emotional functioning* mainly refers to basic abilities such as awareness, expression and regulation of emotions and therefore is not sufficiently operationalized by domains such as depression or anxiety[37], patient representatives of the VAPAIN panel reported that it is more the emotional burden of chronic pain, including anger, grief, distress, anxiety and depressiveness, they want to be changed by IMPT. Because of the heterogeneity of distressing emotions an overarching domain became necessary to capture most of the emotional changes in patients attending IMPT, which was chosen by indicating *emotional wellbeing* as an outcome domain. However, according to a previous survey in patients with chronic pain[38], especially the social as well as the psychological health area were indicated as of highest importance. Including the perspective of patients in establishing core outcome sets means to consider their needs of restoration ability to get back to a personally satisfying life, which always includes biological, at least in terms of functional, psychological and eventually social dimensions.

VAPAIN has followed established guidelines for COS development to enhance transparency of process and results. Further, starting from therapy aims, and involving patient representatives fully in discussion throughout the consensus process of VAPAIN, may have contributed to the differences in outcome recommendations compared to other initiatives[5,37]. The experience of the stakeholders in

comprehensive treatment approaches in chronic pain and the steady awareness of a bio-psycho-social perspective have led to the suggestion of five completely new outcome domains. Above all, a consensus in this subject would not have been accomplished by online surveys, where perspectives cannot be negotiated.

Other issues concern the importance of additional domains, and the associated need to classify outcome-domains in relation to their relevance to specific chronic pain conditions. Since the population of patients with chronic pain in IMPT is frequently heterogeneous, the idea of finding an overarching domain, which covers most of the heterogeneous sample, and is still sensitive enough to measure change, is particularly challenging. This emphasizes the importance of a continuing validation process, after identification of measurement instruments, to investigate overlaps, and distinction of theoretical underlying constructs.

Developing a COS on domains is insufficient to ensure high quality studies in trials and routine care. The identification of reliable and valid instruments will be a critical next step. A shortlist of reliable instruments and validation studies to date, related to outcome-domains, will provide an invaluable resource to clinicians and researchers.

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Legends of figures and tables

Figure 1 Procedure and Regulations of Consensus of VAPAIN

Table 1 **Initial outcome-domains derived from systematic literature review and VAPAIN panel suggestion with voting results from *round 2* of online survey (*step 1, 1.2*)**

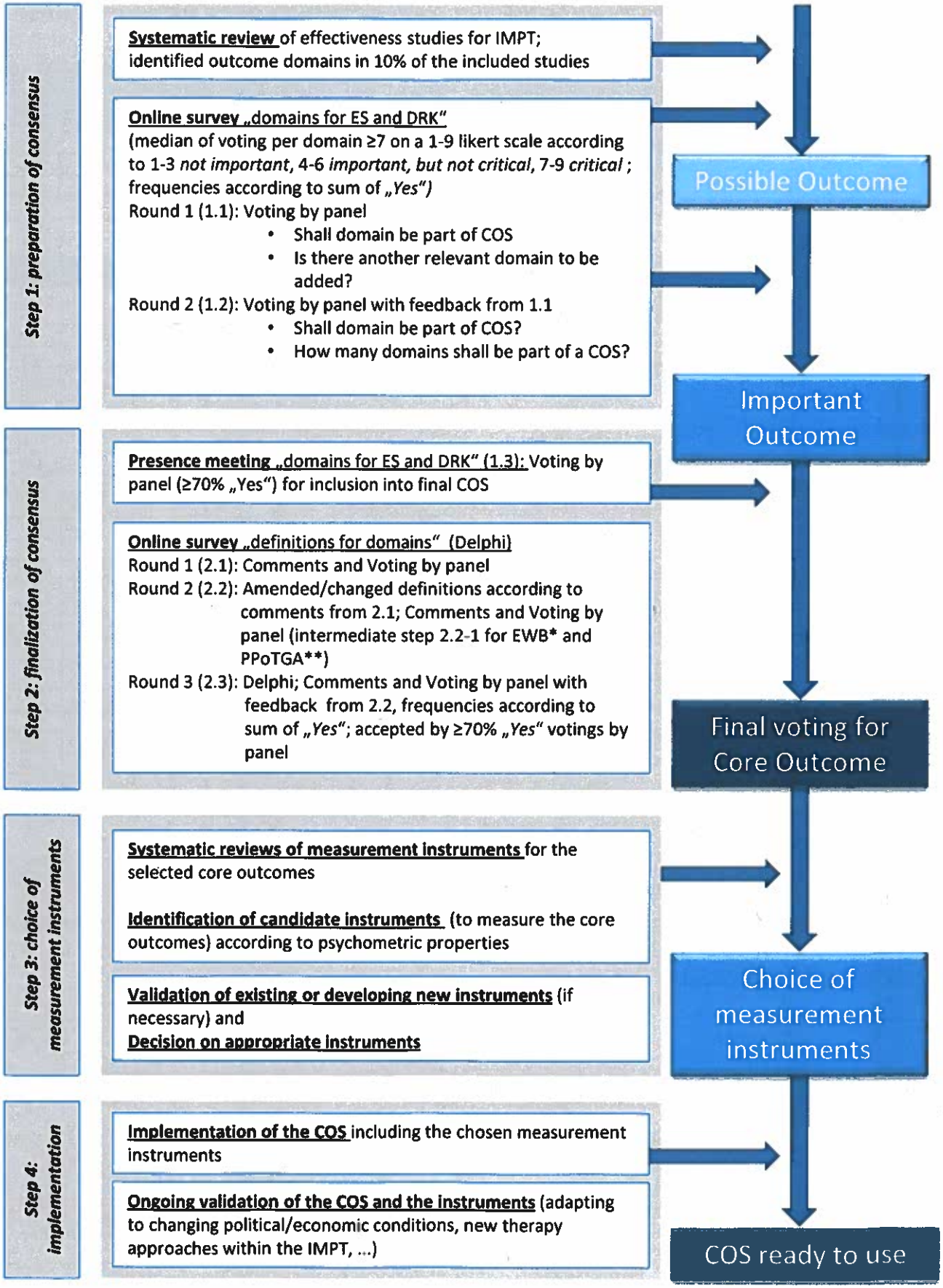
Table 2 **Nominating organizations and professions of the VAPAIN panel members**

Table 3 **Sample size description of the VAPAIN panel members**

Table 4 **Final voting on outcome-domains for IMPT, face-to-face-meeting, *step 2***

Table 5 **Definition of recommended outcome-domains and results of voting from *round 3* online survey (*step 2, 2.3*)**

Figure



*EWB *emotional wellbeing*; **PPoTGA *patient perception of treatment goal achievement*
IMPT interdisciplinary multimodal pain therapy; COS core outcome set; ES effectiveness studies; DRK daily record keeping

Table

Table 1 **initial outcome-domains derived from systematic literature review and panel suggestion with voting results from *round 2* of online survey (*step 1, 1.2*)**

Online survey *1.2* (N=22)			**-daily record keeping- [1-9]**			**-Efficacy/effectiveness studies- [1-9]**		
Core area			**Md**	**min**	**max**	**Md**	**min**	**max**
Derived from Systematic review (step 1)		General quality of life	4,5	1	9	7	3	9
		Health related quality of life	7	1	9	8	7	9
		Sickness impact	4,5	1	9	7	3	9
		Mental health	4	1	8	7	3	9
		Physical health	4,5	1	8	7	3	9
		Social health	4,5	1	8	7	3	9
Domain			**Md**	**min**	**max**	**Md**	**min**	**max**
Derived from Systematic review (step 1)	Physical Health*	Disability in general	4	1	9	7	2	9
		Pain-related disability	7,5	1	9	8,5	3	9
		Functional/physical disability	6,5	1	9	7	3	9
		Pain as a symptom	7	1	9	8	1	9
		Pain intensity/severity	9	3	9	9	5	9
		Pain site	5,5	1	9	7	2	9
		Physical function	7	1	9	7,5	5	9
	Mental Health*	Psychological/emotional distress/strain	7,5	1	9	8,5	3	9
		Depressive symptom	7	1	9	7	3	9
		General fear	4	1	7	5	2	8
		Fear of pain	7	1	9	7	3	8
		Avoidance of movement	7,5	1	9	8	3	9
		General coping	5	1	8	6	3	9
		Pain-related coping	7	1	8	7	3	9
		Pain-related catastrophizing	6	1	9	7	3	9
		General self-efficacy	4	1	8	6	3	9
		Pain-related self-efficacy	6	1	9	8	3	9
	Social Health*	Work ability	7	1	9	7	5	9
		Return to work	5	1	9	8	5	9
		Sick leave	5	1	9	7	5	9
		Actual work status	3,5	1	7	6,5	1	9
Derived from panel by suggestion in step 1, 1.2	unassigned	Patient's individual treatment goals	6	1	8	7	1	9
		Ability to do unpaid work activity	4,5	1	9	6	2	9
		Fatigue due to pain	7	1	9	7	2	9
		Difficulty concentrating due to pain	6	1	9	7	2	9
		Maintain relationships/maintain relationships in the presence of pain	6	1	9	7	5	9
		Confidence to live with pain	5	1	8	6,5	1	8
		Analgesic medication/taken taken analgesics	7	3	9	6	4	9
		Reasons for dropout or withdrawal from treatment	6	1	9	7	1	9
		Daily physical activity	7	1	9	6,5	1	9
		Patients global impression of change	5,5	1	9	7	4	8
		Pain frequency, i.e. attacks in migraine	7	1	9	7	3	9
		Pain diary and medication for at least 4 continuous days	6	1	9	6	1	8
		Body awareness	5	1	8	6	1	9
		Autonom function	5	1	9	5	1	9
		Quality of relationships and engagement in social activities	6	1	9	7	3	9
		Engagement in leisure activities	6,5	2	9	7	3	8
		Use of health care services	7	1	9	7	5	9
		Activities to compensate pain	6,5	1	9	6	1	8
		Personal goal achievement	7	1	9	7	1	9

* referring to PROMIS systematic of self-reported Health outcome areas and domains[29] to ensure bio-psycho-social complexity
Md *Median*, min *Minimum*, max *Maximum*, ES *effectiveness studies*, DRK *daily record keeping*

Table

Table 2 **Participants and Organizations**

	Name of organization/scientific association	n
Physicians	German Pain Society (Chapter of International Association for the Study of Pain)	2
	German Migraine- and Headache Society (DMKG)	1
	European Pain Federation (EFIC)	2
Physiotherapists	Chartered Society of Physiotherapy (C.S.P.)	1
	German Federation of Physiotherapy (ZVK)	1
	AXXON, Physical Therapy in Belgium	1
	Swedish Association of Physiotherapists	1
	Koninklijk Nederlands Genootschap Voor Fysiotherapie (K.N.G.F.)	1
Psychotherapists	German Association for Psychological Pain Therapy and Research (DGPSF)	2
	European Pain Federation (EFIC)	1
	International Association for the Study of Pain (IASP)	2
Researchers	Harmonizing Outcome Measures for Eczema (HOME)	2
	Core outcome measures in effectiveness trials (COMET)	1
	Outcome Measures in Rheumatology (OMERACT)	1
	Consensus-based standards for the selection of health measurement instruments (COSMIN)	1
Patient representatives	German pain league	1
	Patient federation "SchmerzLOS e.V."	1
	German headache league	1
	Pelvic Pain support network	1
	nominated by survey participants	1

Table

Table 3 **Sample size description of participants**

Age (years)	**Mean**		**Range**
	48		29 – 70
Gender	**Gender**		**Number** (Percent of participants)
	Female		11 (44 %)
	Male		14 (56 %)
Country	**Name**		**Number** (Percent of participants)
	Germany		11 (44 %)
	United Kingdom		4 (16 %)
	Netherlands		3 (12 %)
	Belgium		2 (8 %)
	Italy		2 (8 %)
	Canada		1 (4 %)
	Sweden		1 (4 %)
	United States of America		1 (4 %)
Experience*	**N**	**Mean (years)**	**Range (years)**
Professional Experience	20	19	5 - 45
Professional Experience in Current Role	19**	17	2 - 45
** no patients; ** n=19; one missing answer*			

Table

Table 4* final voting on outcome-domains for IMPT, face-to-face-meeting, *step 2

	%			N
	Yes	No	Abstention	
Pain Intensity	87	13	0	23
Emotional Wellbeing	83	9	8	23
Health related Quality of Life	82	18	0	22
Satisfaction with Social Roles and Activities	81	19	0	21
Productivity (at home and at work, paid/unpaid work) including the terms presentism and absenteeism	81	14	5	21
Pain Frequency	78	22	0	23
Patient´s Perception of Treatment Goal Achievement	78	17	5	23
Physical Activity	73	27	0	22
Reasons for Withdrawal/Dropout*	68	32	0	22

** not voted into COS ES but strongly recommended for enhanced report quality*

Table

Table 5 **Definition of recommended outcome-domains and results of voting from *round 3* online survey (*step 2, 2.3*)**

Definition of recommended outcome-domains		Final voting (*2.3*; N=25, 100 %)		
		Agree [%]	Disagree [%]	Abstent. [%]
Pain intensity is defined as how much a patient hurts, reflecting the overall magnitude of the pain experience[11]		100	0	0
Pain frequency is defined as the rate of pain episodes relative to a specified time frame. It can be described by duration, frequency and intensity of attacks of (increased) pain. It might occur on top of background pain or in between pain-free periods [no citable reference available]		68	32	0
Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, & engaging in recreational pursuits[4,22]		100	0	0
Emotional well-being is defined as feeling a preponderance of pleasant rather than unpleasant affect in one's life over time[9]		88	8	4
Health related quality of life is the functional effect of a medical condition and/or its consequent therapy upon a patient. It is thus subjective and multidimensional, encompassing physical & occupational function, psychological state, social interaction & somatic sensation [4,34,3]		80	16	4
Satisfaction with social roles and social activities describes the impact on patient's satisfaction in performing usual social roles and activities (including family and work)[29]		84	16	0
Productivity is defined by the output per unit of input, for example production output per labor hours. It comprises paid and unpaid work as well as home work (e.g., housekeeping, caring for infants or sick relatives)[1]		88	4	8
Sub-domains of Productivity	***Absenteeism*** is defined by days off work comprising paid/unpaid work as well as home work (e.g., housekeeping, caring for infants or sick relatives)[1]	100	0	0
	Presentism is defined by having difficulties/inefficiencies at work, where work is paid/unpaid work, or home work (e.g., housekeeping, caring for infants or sick relatives)[1]	96	4	0
Patient's perception of treatment goal achievement: The own perception of the patient regarding the efficacy of the therapy to achieve the predefined treatment goals [no citable definition available]		96	4	0

Minutes from the face to face meeting of VAPAIN panel

Consideration for or against domains to be part of a Core outcome set to assess effectiveness in clinical trials referring to interdisciplinary multimodal pain therapy in chronic pain patients

- Minutes from the meeting about outcome domains according to physical health-

The panel agreed that *pain intensity* and *pain frequency* should be considered as core outcome domains. Suitable instruments to assess both domains should ideally include information about *pain intensity* as well as *pain frequency*. The majority of panel members emphasized that the sole reduction of *pain intensity* is no primary aim of IMPT and therefore additional outcomes are highly relevant for the COS. Patient representatives and health professionals highlighted that the coping of pain may be more important than the reduction of intensity. According to the differentiation between the terms *physical function, disability* etc. patient representatives claimed to prefer the term *physical activity* because they found much more important what patients really do (*physical activity*) instead of what they are able to do (*physical function*). It was consented in the panel that activity means "what you do" and ability was defined as "what you could do". It was consistently stated that having the ability to perform any kind of activity does not compelling change behavior (for instance a depressive mood or fear of pain keep patients from climbing stairs even though they have the ability and unrestricted function to do so).

- Minutes from the meeting about outcome domains according to mental health-

There were several mental outcome domains provided to the panel members. Especially patients emphasized that not all of them have depressive symptoms or fear of pain. Psychological factors are heterogeneous among the patients and there is none to cover psychological impairment in all of them. Resulting from that situation the challenge was seen in finding a COS ES outcome domain (as a comprehensive endpoint) as to be as specific as possible and as general as necessary. The panel decided to emerge *emotional wellbeing* as overarching endpoint of all possible psychological burdens in patients with chronic pain in IMPT. The close term of mental wellbeing was rejected because mental aspects comprise cognitive factors as well as emotional. The emotional burden of chronic pain was considered highly relevant whereby cognitive impairment was seen to be less relevant in the target population of patients with chronic pain.

IMPT is provided to a very heterogeneous patient sample. Individual goal arrangement was discussed to therefore be an essential part of this therapy approach. The success of IMPT depends strongly on the willingness of the patient to maintain adaptive behavior agreed on during IMPT as well as on the individual goal of the patient. The panel members decided to take the outcome domain of *patient´s impression of treatment goal achievement* into COS ES.

- Minutes from the meeting about outcome domains according to social health-

The outcome domain *satisfaction with social roles and social activities* was stated by patient representatives to be more important than the mere existence of relationships. They emphasized that quality of relationships and activity engagement is essential for patients. Suggestion to call the domain "quality of social relationships" was rejected because aims of IMPT do not mainly include therapeutic work on relationships. Therapy aims of IMPT shall enable the patient to return into social roles and settings by improving function and coping with pain and impairment. Neither settings nor maladaptive schemes are focus of IMPT.

Among all possible outcome domains to picture work specific aspects the panel members debated about the role of work and work related activity. Outcome domains such as *work status* or *work ability* were seen critically because they match working people only. A considerable amount of patients of IMPT does not return to work because of persisting physical limitations and impairments. Besides the aspects of paid work, activities such as house holding, caring for relatives and children and volunteer commitment are existent among IMPT patients and important to those who receive disability pension. The limitations or activities of patients in IMPT affect more than paid work. So the panel defined and finally included the term *productivity (absenteeism and presentism at work and at*

home) as umbrella term for paid and unpaid work to cover patients' situation comprehensively in a COS ES.
- Minutes from the meeting about health related quality of life (generic outcome domain)-
The outcome domain *health-related quality of life* was discussed to comprise a very broad concept with a lot of aspects and hence limitations in application. Another argument was a possible redundancy since the emerging COS ES already includes different bio-psycho-social aspects.
- Further minutes from the meeting -
With 68% just under the threshold for being included *reasons for withdrawal/dropout* was rejected as COS domain. Despite, the panel emphasized that *reasons for withdrawal/dropout* should be consistently reported for every single study and reflect reporting quality of ES studies in IMPT. The meaning of "recommended" domains became more tangible when considering condition specific outcome domains referring to a subgroup of chronic pain patients. E.g. *fear of pain*, frequently found in patients with chronic (low) back pain, could be a recommended outcome domain to accomplish the COS ES in this specific condition. Unfortunately this important discussion was unfinished because of the lack of time.
Abbreviations: IMPT interdisciplinary multimodal pain therapy, COS core outcome set, ES effectiveness studies