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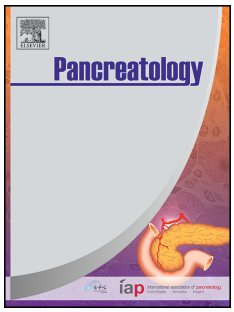

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Assessment of pain associated with chronic pancreatitis: An international consensus guideline

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Abstract

Pain is the most common symptom in chronic pancreatitis (CP) with a major impact on quality of life. Few validated questionnaires to assess pain in CP exist, and the lack of consensus negatively impacts clinical management, research and meta-analysis. This guideline aims to review generic pain questionnaires for their usability in CP, to outline how pain assessment can be modified by confounding factors and pain types, to assess the value of additional measures such as quality of life, mental health and quantitative sensory testing, and finally to review pain assessment questionnaires used specifically in CP. A systematic review was done to answer 27 questions that followed the PICO (Population; Intervention; Comparator; Outcome) template. Quality of evidence of the statements was judged by Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria. The manuscript was sent for review to 36 experts from various disciplines and continents in a multi-stage Delphi process, and finally reviewed by patient representatives. Main findings were that generic pain instruments are valid in most settings, but aspects of pain are specific for CP (including in children), and instruments have to account for the wide phenotypic variability and development of sensitization of the central nervous system. Side effects to treatment and placebo effects shall also be considered. Some multidimensional questionnaires are validated for CP and are recommended together with assessment of quality of life and psychiatric co-morbidities. This guideline will result in more homogeneous and comprehensive pain assessment to potentially improve management of painful CP.

Introduction and methods

Epidemiology: The prevalence of chronic pancreatitis (CP) is unknown, but estimated to be as high as 150/100,000(1,2). The disease is likely underdiagnosed as in many places only patients with acute on chronic pancreatitis, or those with the most severe symptoms (end stage disease) are referred for clinical investigations. Abdominal pain is the most common symptom of CP, hereafter called "pain associated with chronic pancreatitis (PACP). PACP is observed as the initial presentation in ~75% of patients(3), and is present during the clinical course of disease in 85-97%(3–6). In a recent European cross-sectional study including 1384 patients with CP, about 60% suffered from pain(7). Pain varies widely during the clinical course of disease, and about 40% of patients report intermittent pain, and 60% constant pain(8). Phillips et al. recently reported that patients with anxiety or depression were more likely to describe constant or intermittent pain as opposed to no pain, and this underscores that constant pain may reflect complicated disease(9). The temporal pain pattern may, however, not be consistent and it was recently shown that about 60% alternate between pain patterns when observed over a 4 year period(10). The impact of pain in patients with CP is massive, and is the most frequent cause for hospitalization and the strongest predictor of poor quality of life(8,11,12).

Pain mechanisms: Pancreas is a densely innervated organ and the nerves are involved in a variety of physiological functions associated with the glandular structure and hormonal functions. The nerves are therefore prone to damage of the parenchyma. CP is characterized by inflammation of the pancreas that results in replacement of the glandular tissue with fibrosis. This leads to progressive exocrine and endocrine insufficiency, but also to pancreatic neuropathy with pathophysiological changes. Experimental and human studies have provided evidence for pancreatic neuropathy and neuroplasticity at both the peripheral (pancreatic gland) and central level of the sensory system, for details see(13,14). These changes resemble to a high degree that seen in neuropathic pain disorders (13). Along this line, pregabalin, a drug that has shown its effectiveness in neuropathic pain, was shown to be effective in PACP in a randomized placebo controlled trial(15). Although neuropathy is clearly involved, the detailed mechanisms responsible for producing PACP are unclear. Pain is likely heterogeneous and multiplex, representing different drivers (anatomical, inflammatory, neurobiological, psychosocial), locations (peripheral, central), and confounding factors (pharmacological interactions, psychiatric comorbidity etc.)(16). Pain can be related to status of the pancreas (e.g. acute or chronic inflammation, pancreatic ductal obstruction from stones and/or stricture), peripancreatic structures (e.g. common bile duct stricture, gastric outlet or duodenal obstruction) and/or local complications (e.g. pseudocyst). However, little association exists between pain and morphological characteristics(17,18), and other factors clearly play a leading role in individual patient's pain experience.

Recent studies using quantitative sensory testing (QST) have indicated that central sensitization is present in about 50% of patients with CP(19). This supports the variability of pain mechanisms between patients and helps to explain differences in treatment response. Thus, patients with major central sensitization are less responsive to treatment(14). Improved methods of pain assessment are therefore necessary in order to select appropriate patients for different treatment options, and the development of pain biomarkers to predict the individual patient response are needed.

Nature of PACP: PACP is variably described as a dull, sharp or nagging sensation in the upper abdomen with or without radiation to the back. Patients with early onset-disease and those with alcohol aetiology are more likely to suffer from pain(1). Clinically, the early stage of CP is typically dominated by pain attacks associated with recurrent episodes of pancreatitis and local or systemic complications. In contrast, more established CP is typically responsible for more constant pain(8). According to the *burn-out* hypothesis, a majority of patients becomes pain-free later in the course of CP(4,20). This hypothesis has not been proven and persistent pain in occurs in a significant fraction of patients even after 10 or more years of disease(21). PACP often presents after or is worsened by food intake (postprandial pain). Continued alcohol consumption is linked with disease progression(22), and increases the frequency of pain episodes(23). Although no empiric data specifically associates tobacco smoking to pain, given the role of tobacco in disease progression(24), it is conceivable that it may have an indirect and negative effect on pain.

Pain assessment: The assessment of pain has not been a significant feature of guidelines relating to the management of CP. It was briefly mentioned in a previous European guideline(25) and an international guideline for pain management of CP described current instruments to assess pain(16). There has now been a comprehensive review of the multiple instruments used to assess pain (16) (26), but only few were developed specifically for CP. Such a pain assessment instrument will need to account for the wide phenotypic variability, detect the development of central sensitization and features of chronic pain in general. Pain is a complex sensory experience including evaluative, cognitive and affective components, and a pain assessment instrument should therefore measure the different dimensions of pain(27). Depending on the research question it should include phenotypic domains such as psychosocial factors, symptom characteristics, sleep patterns, responses to noxious stimulation, endogenous pain-modulatory processes, and response to pharmacologic challenge.

The lack of a standardized and validated pain assessment instrument for CP is a significant unmet need and negatively impacts both clinical management and research design(28). Better pain assessment will make it possible to monitor clinical management of PACP in a more reliable way and to optimize trials in patients with PACP, and more accurately record the response and outcome treatment. Finally, such an instrument may serve as a template on how to assess pain and associated symptoms in other gastrointestinal disorders, and pave the road to improved symptom assessment in gastroenterology in general.

Aims:

The aims of this guideline for pain assessment in patients with CP are:

1. To review the **generic pain assessment instruments** and how they relate to PACP.
2. To outline how PACP can be modified by **confounding factors** and **pain types** including a) the effect of placebo and nocebo on pain assessment, b) side effects of interventions, and what specific factors should be considered in the settings of c) different CP phenotypes, d) pain in children and e) acute pain.
3. To review the value of **quality of life, mental health** and **quantitative sensory testing** in assessment of PACP

4. To review **pain assessment questionnaires** in relation to PACP and how these can be applied to clinical practice and research.

Methods

The study was endorsed by the European Pancreatic Club. As no management recommendations were used in this guideline, disclosures were not considered relevant. The workflow is shown in figure 1 and included formation of a working group consisting of a multidisciplinary team of gastroenterologists (AMD, SSO), surgeons (SAWB, HvS, MGB, CvV, JAW), a paediatrician (MDB) and a psychologist (LV). An Expert Panel was invited for consensus ratings using a modified Delphi method. These 42 specialists were widely distributed across the continents and were appointed to represent worldwide specialists in treatment of pancreatic pain. These included representatives from gastroenterology, endoscopy, surgery, pain medicine and psychology. Three specialists did not find time to participate, one was reluctant to the rationale for the work and two did not reply to the emails, leaving 36 specialists for the final Expert Panel. Importantly, none of the participants in the Working Group or Expert Panel had any conflicts of interest with respect to pain assessment.

----------Figure 1 near here----------

The working group drafted a template for the different sections in the guideline and formed the first version of the questions to be considered. Next a **systematic literature search** was done by SAWB and CvV focusing on pain assessment in PACP where the **PRISMA** (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were followed including checklists for the reviewed papers(29). The search language was restricted to English literature and performed in the fall 2019 with an update in summer 2020 using EMBASE, Medline and Cochrane library. The literature review was updating the recent search by Teo et al.(26) with the Mesh terms: chronic pancreatitis AND every possible known intervention for chronic pancreatitis i.e. ‘alcohol abstinence’, ‘analgesia’, ‘antioxidants’, ‘surgery’ and ‘endoscopy’, and the information flow is shown in figure 2 (30), where the AIIMS and SF-COMPAT (see later) were included after the search. Detailed information of the interventions used in the different studies is shown in Table 1. After written consensus in the Working Group, subgroups were formed, each charged with updating recommendations in specific areas and questions were refined to follow the **PICO** (Population; Intervention; Comparator; Outcome) template(31,32). PICO is most frequently used in traditional quantitative reviews, but can be modified to include qualitative evidence(33). The background text for the summary sections was drafted and during this process, subsequent meetings between subgroups and key individuals, teleconferences and email discussions were done. Whenever needed, a separate search was performed for each defined question. The committee chair (AMD) worked with subgroup heads to ensure homogeneous and comprehensive outline of the document. Quality of evidence was judged by predefined Grades of Recommendation, Assessment, Development and Evaluation (**GRADE**) criteria(34). The GRADE system was chosen even though it is mainly used for evaluation of the evidence in different diseases. However, with modifications it

is also applicable for diagnostic tests and strategies, although vulnerable to limitations and suspect to indirect evidence(35). Significant education of committee members on the GRADE approach was performed via e-mail and tutorials (as adapted for "UpToDate" (http://www.uptodate.com/home/grading-tutorial).ref) before the text was written. In the absence or limited availability of literature, the Pain Management Working Group decided if a recommendation would be included in the consensus report.

----------Figure 2 near here----------

----------Table 1 near here----------

The **quality of evidence** supporting the different statements was graded as (i) "high" if there was very low probability of further research completely changing the presented conclusions, (ii) "moderate" if further research may completely change the conclusions, (iii) "low" if further research is likely to change the presented conclusions completely. The term "very low" (iv) could be used if new research will most probably change the presented conclusions completely; however, the term was not used in the present work. Following adequate discussion and assigning strength of evidence, the subgroups agreed by email on a draft proposal for the guidelines. This included preliminary **recommendations** (strong, weak, conditional) for the questions according to GRADE guidelines. Implications of calling a recommendation for "strong" was that most well-informed patients would accept that intervention and that most clinicians should use it in most situations. A weak recommendation in favour of an intervention indicated that the desirable effects of adherence to a recommendation probably will outweigh the undesirable effects, but the panel is not confident about these trade-offs. This draft was presented at a meetings in the Working Group 8th December 2020 for general discussion of the quality of evidence and recommendations for the statements. After this meeting the wording was rephrased and send out for review off-line At the discretion of the chair and following adequate discussion, competing proposals for wording of recommendations or assigning strength of evidence were resolved by formal voting. A strong recommendation was worded as "we recommend", a conditional recommendation as "we advise" and a weak recommendation as "we suggest".

The revised manuscript was edited by the members of the Working group by email and send for external review to the Expert Panel for ratings of strength of recommendation in a modified, interactive and multi-stage Delphi process. This was used to ensure both depth and breadth of review in an iterative anonymous voting method(36). In this process the questions were evaluated by the members independently in private. As the panel (on purpose) was spread around the world, face-to-face meetings were not possible due to the ongoing Corona pandemic and voting's were done by email. Video conferences with the chair of the Working Group were used whenever needed to resolve any questions from the members of the Expert Panel. All participants in the Expert Panel voted on their level of agreement with the preliminary recommendations and evidence on a 9 point Likert scale from 1, 'strongly disagree', to 9 'strongly agree' (figure 3) on 28 questions. Voting results were classified under "agreement" as either; strong (80% of votes were 7 or above),

conditional (65% of votes were 7 or above), or weak (less than 65% of votes were 7 or above)(16). If experts did not vote for a specific question it was resent for a new voting to be included in consensus tabulations. The Delphi round was associated with comments and discussion by email, and it was concluded that the question 25 was deleted as it was redundant to the question about pain assessment in general. Questions where agreement with the recommendations were weak or conditional (n=6) were rephrased by the Working Group and send to the Expert Panel in the second round of the Delphi Process. In this round where discussions were done as in first round, Q10,12,16,21,23 and 27 all were rated "Strong".

----------Figure 3 near here----------

After the Delphi process patient representatives evaluated and commented on the final draft of the document. Finally, the Working Group met again virtually to resolve any disagreements and discuss any translations to other languages as well as construction of an App. A short version (about 4000 words) was made and circulated to all authors in the Working group for final editing and approval.

Pain assessment instruments in general

Studies are only as credible as the quality of the outcome measures(37). Pain is the most common presenting complaint associated with CP, and the most important subject of treatment and endpoint for clinical outcomes and trials. Although PACP have certain characteristic features, it is important to consider what is recommended for pain assessment in general across different conditions associated with pain. This section describes what is recommended for assessment of pain in general and its impact on PACP.

<u>Question 1</u>: Is there a need for a multidimensional pain questionnaire to standardize outcome assessment in clinical trials in patients with PACP?
Answer: We recommend pain questionnaires to address multiple dimensions of pain and associated symptoms, and to standardize outcome assessment in clinical trials in patients with PACP.
Quality assessment: High
Recommendation: Strong
Agreement: Strong

Comments: Pain is a subjective experience, and pain intensity is typically a key assessment parameter. However, when pain becomes chronic then affective, evaluative and cognitive components assume greater importance. This was already highlighted in a keynote paper more than 100-years ago(38). Several studies have shown that changes in pain severity do not necessarily track with patients ratings of improvement and satisfaction(27,39,40). In other words the overall well-being of a patient after treatment is not dependent on pain intensity alone. Therefore, the traditional one-dimensional pain intensity ratings (e.g. visual analogue scales or numeric rating scales) are clearly insufficient in chronic pain, and there is need for a more comprehensive (i.e.

including multiple domains) and standardized approach to pain assessment. This is also reflected in other diseases such as cancer pan, and it has been documented that failure to conduct a multidimensional assessment likely plays a significant role in under-treatment of cancer pain(41). This approach fails to appreciate the multiple other dimensions of the pain experience(42–44). Finally, the pain profile of alcohol induced CP with cognitive and emotional deficits versus non-alcoholic causes of CP are different and require different multidimensional pain questionnaires(45–49).

<u>Question 2:</u> Can the core and supplementary domains in the IMMPACT ('Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials') guidelines be used to optimize the design of pain questionnaires to be used in clinical trials of patients with PACP?
Answer: We advise the use of the IMMPACT guidelines to assess individual pain characteristics, although further work is required to validate some of the domains in patients with PACP.
Quality assessment: Moderate
Recommendation: Conditional
Agreement: Strong

Comments: There is a need to clear up the situation of heterogeneous and therefore incomparable outcome measures that makes it difficult to compare trials and decrease the quality of meta-analyses. Development of such "core domains" was pioneered by OMERACT (Outcome Measures in Rheumatology)(37), stressing that criteria of truth (i.e., validity), discrimination (i.e., reliability and sensitivity to change) and feasibility should be the framework for all outcome measures. There has since then been a number of projects to identify different domains relevant to the assessment of chronic pain. One such project was the "Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials" (*IMMPACT*), which was undertaken by a working group of 27 people representing academia, governmental agencies, and the pharmaceutical industry. The first consensus meeting defined 6 core domains that should be used in clinical trials of pain across different diseases(27). The aim was to construct a set of outcome domains and measurement procedures to minimize the major variability clinical pain trials in order to facilitate comparison and pooling of data between trials, encourage more complete investigations and reporting of relevant outcomes. The following domains were considered to be the most important for chronic pain (details are described in (5),(50),(51):

1. *Pain* is listed as the first outcome measure. However, there are many dimensions of pain such as intensity, location, specific descriptors and qualities that could be taken into consideration.
2. *Physical functioning* is another key outcome, and includes multiple domains of functioning, including behaviour, mood, satisfaction and health related quality of life (HRQOL).
3. Chronic pain is often associated with *emotional distress*, manifested as anxiety, depression, anger, and irritability. Although less well-defined than domains such as pain intensity, a number of different instruments have been developed to assess these dimensions of pain.

4. *Global evaluations* are mandatory to assess the individuals overall improvement, and is often the primary endpoints in clinical trials as it is easy and is related to most other domains.
5. *Adverse events* are recorded in most clinical trials, especially when analgesics are involved, and addiction and physical dependence must also be included.
6. *Participant inclusion*: All participants screened for a clinical trial should be carefully described (disposition) according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines(52), and any deviation to the protocol registered.

In addition to these 6 outcome domains, there were 8 supplemental domains (Table 2) to be considered in clinical trials. When PACP is linked to alcoholic aetiology, cognitive and social functioning significantly impacts on their representation of the pain, and the first two supplemental pain domains could be added to the six primary IMMPACT domains as essential components of the pain questionnaires.

----------Table 2 near here----------

In 2016 Edwards et al. (53) described additional core *phenotypic characteristics for pain patients* with the potential to be used for prediction of treatment response. These were psychophysical measures, pain qualities, sleep, quantitative sensory testing (QST), conditioned pain modulation (normally also considered QST) and pharmacological challenge. Along with these core domains, recommended measures were discussed. For e.g., the psychophysical phenotype, the questionnaires were: Hospital Anxiety and Depression Scale (HADS), Pain Catastrophizing Scale (PCS) and Patient-Reported Outcomes Measurement Information System (PROMIS) subscales. Most of these instruments were previously shown to predict treatment responses, for details see(53).
The IMMPACT approach has been successful in allowing the Food and Drug Administration (FDA) to define outcome measures for pain trials that could lead to approval. Part of this approach, requires an externally-led patient-focused drug development meeting with a summary statement called “Voice of the Patient”(ref). Hence, FDA and IMMPACT representatives have started the process of defining such outcome measures(54).
Current use of analgesics have not been included in most pain questionnaires, although the need for rescue medication was a measure of pain intensity in the IMMPACT guidelines(50). The reason is likely that most outcome measures were designed for trials of analgesics or multidimensional pain management, where it is recommended to keep the basic analgesic dose constant during the treatment period. The relevance of medication was also highlighted in the patient centred interview study by Casarett et al.(55), where a decrease in pain intensity, opioid dose and frequency of scheduled analgesic dose were considered the most important endpoints out of 20 statements. Similarly use of medication is a core outcome in the German Pain Questionnaire(56), and likely patients who require strong analgesics have higher pain intensity or more complex disease and decreased coping mechanisms as compared with patients who only uses analgesics on demand. For

studies in PACP use of treatment is highly relevant, and medication was included in the Izbicki score(57), the M-ANNHEIM grading of clinical features of CP, and the AIIMS pain score(58,59). Although no systematic studies have used the IMMPACT guidelines in PACP, it is plausible that they can be used to optimize assessment. For example the HADS was recently used to quantify anxiety and depression in PACP(9). When considering assessment of PACP it is also important to stress that variability in clinical presentation and underlying pain mechanisms is greater between patients than between different pain syndromes (51). This indicates that mechanistic aetiologies such as central sensitization dominate the clinical picture and the peripheral drive becomes less important irrespective of whether it originates in visceral or somatic structures(60). Therefore subsequent assessment and treatment is likely to be based at the level of the individual rather than at the level of the disease. This validates the use of pain assessment recommendations in general for PACP(53).

One important concern is that questionnaires may be too long and time consuming, which of limited utility for routine clinical use. While it is important to assess pain in different domains in clinical trials, it is equally important to have simple outcome measurement in these settings. If it is made too complex, the assessment is difficult and generalizability of results is limited. Hence, patients with chronic pain such as PACP, and long term opiate users often struggle to concentrate for significant lengths of time especially when tasked with completion of complex and multipage questionnaires. This is addressed in the section "Chronic pancreatitis specific pain questionnaires" with questions 25-28.

<u>Question 3:</u> Can the core domains from the IMMPACT guidelines be quantified and combined in a meaningful way to assess patients with PACP?

Answer: We suggest that the core domains from IMMPACT guidelines can be quantified and combined in a meaningful way for the assessment of patients with PACP, with a mixture of different questionnaires depending on the specific research question.

Quality assessment: Low

Recommendation: Weak

Agreement: Strong

Comments: To address the core and supplemental domains from IMMPACT guidelines it is necessary to select and combine specific questionnaires. The characteristics of the questionnaires need to be considered, and in particular for reliability, validity, responsiveness to change, feasibility and participant burden, practicality within the clinical trial settings (37), need for normative data and linguistically/culturally validated versions. The work by Dworkin et al. (61) used a review of the literature and consensus between specialists to recommend which questionnaires should be used for 4 (out of the 6 above) most important domains from the IMMPACT (Table 3).

----------Table 3 near here----------

For use in clinical trials, it is necessary to determine the criteria for what shall be considered *clinical important changes*. Therefore, the same group later defined what should be consensus for the recommended assessment tools within the first 4 core measures (61). The key provisional benchmarks are shown in Table 3, column 2 (61). Some of the same quantifications of responses and assessments of relevant changes have been used in clinical trials of PACP, where they have been able to detect relevant and meaningful responses, see e.g.(15,62–64), and we believe they are valid in this context as well.

<u>Question 4:</u> Are additional questions (such as satisfaction with social roles, productivity and patient's perception of treatment goals) needed to evaluate specific treatments or pain conditions in patients with PACP?
Answer: We recommend that additional questions (such as satisfaction with social roles, productivity and patient's perception of treatment goal) are developed to evaluate specific treatments or pain conditions in patients with PACP
Quality assessment: Moderate
Recommendation: Strong
Agreement: Strong

Comments: A limitation of the original IMMPACT initiative is that *patient representatives* had not been included, as patients suffering from chronic pain may indicate other outcome domains as more important(65). A study by Turk et al.(66) showed that although patients reported outcome domains in general were consistent with the IMMPACT guidelines, they also expands by highlighting domains such as fatigue, sleep, home and family care, social and recreational activities, interpersonal relationships, and sexual activities. It has also been criticized that no systematically literature search or consensus process was done in the IMMPACT guideline. A recent review outlined all the multidimensional outcome tools that have been suggested for chronic pain(67). Lacking methodological quality is a well-known problem in the field of measurements and affects most of the instruments in pain research. The work of the COSMIN group addressing overall health-related patient-reported outcomes is therefore promising(68,69). They recommend that existing scales should be carefully investigated according to their psychometric properties, and that methodological standards need to be reinforced by validation studies taking into account patients' perspectives. One such initiative is the VAPAIN (validation and application of patient reported outcome domains to assess in multimodal pain therapy) that targets to asses effectiveness of an interdisciplinary therapy of chronic pain(65). The authors used a 3-stage consensus study with a mixed-methods approach including several steps of systematic reviews done by a panel including patient representatives. They identified 140 different outcome domains. This was followed by an iterative multistep consensus process on which domains and instruments were identified(70). The panels final consensus was that 8 domains should be included into the core outcome measures for this specific treatment approach. These were: pain intensity, pain frequency, physical activity, emotional well-being, 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.
Economic impacts due to inability to work also may affect pain reporting especially in regions where the social security network is not covering the loss of income. This can lead to a cascade effect where there is a second hit on some domains, not directly related to the pain, but precipitated by economic misfortune(71). Future studies will address the validity of these domains, but the initiative highlight that specific treatments may require different outcome measures such as in PACP. Disease patient-reported outcome measures have not yet been developed, but attempt have been done in exocrine pancreatic insufficiency(72,73). The "Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer" is also using patient-reported outcome measures together with global health instruments in their ongoing studies(74).

Common for all pain conditions is central sensitization as a consequence of the chronification following long-lasting pain. Specific questionnaires have been developed to assess this(75,76), and although not tested in PACP they may be helpful in assessment of specific patient populations. When alcohol aetiology is addressed, further emotive functioning assessments can be added to determine alcohol dependence characteristics. A separate research questionnaire can be considered adding validated tools such as emotional facial expressions recognition deficits(49).

Question 5: Are recommendations for primary, secondary and explorative endpoints in clinical trials for pain patients in general also applicable to patients with PACP?
Answer: We recommend that primary, secondary and explorative endpoints used for pain in general are also used for studies of patients with PACP.
Quality assessment: High
Recommendation: Strong
Agreement: Strong

Comments: With several core measures, the problem with multiple endpoints and type-1 errors arises. This was addressed by the IMMPACT consortium in a publication where statistical handlings of primary and secondary endpoints were addressed(77). The primary endpoint will most often be change in pain intensity or relief, but a composite of many individual measurements such as from a questionnaire can also be used. Some of the recommended core measures such as Brief Pain Inventory (BPI) are in reality composite measures. However, as the reliability and validity of the total and subscale scores are well established, these measures were considered single outcome measures in the IMMPACT recommendations. Some trials may require multiple primary endpoints, but then needs to be tested with a significance level corrected for multiplicity. Secondary endpoints typically are used to provide pain mechanisms, greater understanding of the study etc., and endpoints can also be explorative, for details see(77). These recommendations are considered valid for all patient with pain including PACP. Finally, study endpoints must be carefully considered taking into account the characteristics of the patient population which will be recruited into a given study, and additional endpoints may be needed. For example, the cognitive and emotive disorders

linked to alcohol dependence are different from patients with chronic pain that has no prolonged history of alcohol abuse, and in some studies this needs to be taken into consideration(49).

<u>Question 6:</u> Can standards for optimising the outcome of clinical trials for pain in general such as pain characteristics (e.g., pain duration, intensity, variability) and study design (e.g. cross-over, enriched enrolment) also be used in patients with PACP?
Answer: We recommend that the same standards used for optimizing the outcome of clinical trials in patients with pain in general are used in patients with PACP.
Quality assessment: High
Recommendation: Strong
Agreement: Strong

Comments: The effect in clinical pain trials for e.g., analgesics has been very low, and to increase assay sensitivity, recommendations for the four most relevant domains (factors for patients, study design, study site and outcome measures) in clinical trials were published(78). The most relevant characteristics are shown in Table 4. Different standards were proposed, among these that pain duration should minimum be three months in trials of chronic pain and pain intensity higher than 4 (3-5) on the numeric rating scale. Other factors such as dosing strategy, length of baseline period and trial period were also considered, together with number of sites, recruitment methods etc. The effects of these characteristics on the 6 core measures originally defined(79) were also discussed, and undoubtedly such practical aspects of clinical trial conduct can enhance assay sensitivity.

----------Table 4 near here----------

In order to further optimize IMMPACT guidelines for use in clinical trials, Gewandter et al. made recommendations in regards study design, site selection and staff training, participant selection and training, treatment adherence, data collection, and data and study monitoring(58). For example, sites should be selected according to previous experience, expertise regarding unique populations or study procedures, lists that could identify low performing sites and implementation of staff training. When such considerations are taken into consideration more sites can be included to utilize the strengths of multi-centre trials. Other factors such as quality of life (may be more important than pain intensity) and opioid dose/duration can also be taken into consideration. For assessment of quality of life see section “Comorbidity and quantitative sensory testing”. Such recommendations are also valid for trials of PACP and researchers should be encouraged to familiarize with these standards before they design their clinical trials. However, in PACP specific factors such as recurrent acute on chronic inflammation with recurrent pain can make it difficult to determine duration, and trials shall be designed according to such disease elements.

Question 7: Can a patient's "pain phenotype" be defined by subjective ± semi-objective methods and used to individualize treatment of patients with PACP?
Answer: We advise that "pain phenotyping" defined by subjective ± semi-objective methods is used in clinical trials as an attempt to individualize treatment in patients with PACP.
Quality assessment: Moderate
Recommendation: Conditional
Agreement: Strong

Comments: The core phenotypes described above focuses on what can be subjectively measured, but to determine the pain phenotype other tests may be considered such as motional facial expressions recognition deficits(49) and cognitive tests such as intra-extradimensional set shift and reversals(80). However, more *objectively characteristics* (e.g., functional magnetic resonance imaging (fMRI), electrophysiology etc.) likely also play an important predictive role in pain evaluation and treatment. This was reviewed by Smith et al. (81) with focus on QST, imaging and skin biopsy biomarkers. Of note QST is dependent on subjective evaluations of sensory experiences and does not meet the strict definition of an objective biomarker. However, QST has been shown to be diagnostic across different functional and inflammatory conditions associated with pain. It can also be used to predict the effect of analgesics and non-pharmacological treatment in volunteers and in patients subjected to surgery(81,82). Pharmacodynamically, QST also showed its value and, although not in patients with PACP, tapentadol treatment was for example associated with an improvement in conditioned pain modulation and segmental sensitization (see later)(83,84). In patients with PACP it was also shown that those with response to pregabalin had evidence for more segmental nervous system sensitization(85), and improved conditioned pain modulation(86). Such finding were also seen for skin biopsies in patients with neuropathic pain as well as for imaging, although less convincing(81,87). Other objective biomarkers such as electrophysiology(88) and inflammatory markers(89) have also been used successfully(90), and future studies are needed to standardize these tools and gather data on their measurement properties in PACP.

Question 8: Should the reliability and validity of instruments (including questionnaires) to assess PACP be examined before they are used in clinical and research settings?
Answer: We recommend that reliability and several different validity dimensions of instruments (including questionnaires) are examined and confirmed before they are used to assess PACP.
Quality assessment: High
Recommendation: Strong
Agreement: Strong

Comments: For pain instruments in general, *reliability and validity* of the core outcomes in the questionnaire are key parameters, although discrimination, feasibility and other characteristics are also mandatory to make them attractive for use in large scale(37). Below are the most important validity measures, for detail the reader is referred to(91). Four main validity measures are construct, content, face and criterion validity. *Construct validity* is "the degree to which a test measures what

it claims". Convergent and discriminant validity are the two subtypes of validity that make up construct validity. Convergent validity refers to the degree to which two measures that theoretically should be related, are in fact related, whereas discriminant validity tests whether measurements that are supposed to be unrelated are, in fact, unrelated. *Content validity* is a systematic examination of the test content to determine whether it covers all facets of a given construct, such as whether a pain questionnaire have items covering all relevant areas of pain discussed in the scientific literature. Typically, a panel of experts are used to review the test specifications and selection of items. The term *face validity* assesses whether the test "looks valid" to the examinees, and some people use the term to refer only to the validity of a test to observers who are not expert in testing methodologies. *Criterion validity* is the extent to which a measure is related to an outcome and is often divided into concurrent and predictive validity. Concurrent validity refers to a comparison between the measure and an outcome assessed at the same time, whereas predictive validity compares the measure with an outcome assessed at a later time. Of cause one shall be cautious not to overregulate procedures by always requiring validation and withholding some instruments when they are not yet sufficiently validated. In fact only few questionnaires in pain research have been tested for all validity dimensions, and in PACP only the Short-Form Comprehensive Pain Assessment Tool (COMPAT) has been fully validated(92).

In *experiments* (as opposed to clinical use) the validity of the design is a fundamental part of the scientific method. Internal validity is an estimate of the degree to which conclusions about causal relationships can be made within the context of a particular study. External validity is the extent to which results can be generalized for example to different people, places or times.

Of note it is a challenge when questionnaires are designed for clinical or research purposes in one language, some of the subtleties may be lost when the questionnaire is translated into another language. This may make international comparisons of outcomes less reliable. It is frequently difficult to find a precise translation that conveys exactly the same message across different languages, but at least two multidimensional pain assessment tools are validated in multiple languages: the Brief Pain Inventory (Short form) and McGill Pain questionnaire(93).

Confounding factors and specific pain types

a) Placebo responses and the importance of sham control

<u>Question 9:</u> Should placebo-related factors be controlled to improve evaluation of treatment outcome in randomized studies with new medication for PACP?

Answer: We recommend that placebo-related factors are taken into account in randomised studies testing new treatments for PACP.

Quality assessment: High

Recommendation: Strong

Agreement: Strong

Comments: In pharmacological studies in PACP, presumed active treatments are typically tested against inactive placebo. Meta-analyses of the placebo arm of these trials find an abdominal pain remission rate of 20%, covering a heterogenic range from 2.4% to 50%(94) illustrating that the placebo response is not uniform but highly variable(95,96). Although these data are not controlled for the natural history of the pain and thereby regression towards the mean(97), they suggest that expectations contribute to PACP, which is in line with findings on changes in central processing of pain signalling in the disease(28,94,98).
This hypothesis is confirmed in pharmacological studies in general, where it is well known that positive expectations of treatment outcome can double the pain-relief of analgesics, whereas negative treatment expectations may block the effect(99). Hence, analgesics cannot be approved for clinical use without showing superiority to placebo treatments in clinical trials. Yet, in interventional trials using endoscopy or surgery, less attention has been paid to the influence of expectations(100–102), even though patients' expectations and the placebo component of the treatment appear to increase with the invasiveness of the interventions(96,100–104).

<u>Question 10:</u> In interventional (endoscopic and surgical) studies of patients with PACP is it appropriate to use a sham control group to determine the placebo effect?
Answer: We suggest that a sham control group is used in endoscopic studies of patients with PACP, although this remains very difficult in surgical studies.
Quality assessment: Moderate
Recommendation: Weak
Agreement: Strong

Comments: Sham control of endoscopic stenting of the pancreatic duct to reduce PACP is possible(105), which has been shown in patients with other painful conditions relating to the biliary tree with a placebo response following sham endoscopic intervention of 20-30%(105). In the absence of sham control, this effect may erroneously be attributed to endoscopic stents(102,105,106), so in order to determine whether PACP patients actually benefit from endoscopic interventions or whether they are subjected to unnecessary risks, it is essential to conduct sham controlled trials(102,105,106). A sham-controlled trial combining endoscopic and extracorporeal shock wave lithotripsy in patients with PACP and stones in the pancreatic duct is currently ongoing in India, but due to the current COVID-19 pandemic only few patients have been enrolled(107). Another ongoing pilot trial from South Carolina is in progress and aims to compare endoscopic ultrasound with endoscopic interventions(108).
Endoscopic sphincterotomy has been tested against a sham procedure in patients with sphincter of Oddi dysfunction, and no difference was found between the active and the sham intervention(109). This is in line with previous sham-controlled surgical trials of various chronic pain conditions(110,111). In fact, the patients in the sham conditions in the sphincter of Oddi dysfunction trial did better at follow-up(112); this highlights how patients' expectations, the quality of the patient-provider relationship, the invasiveness of the intervention and the expert context contribute to the overall outcome of a treatment(96,106,112).

Ethical and practical concerns of whether people are willing to participate in invasive and risky sham interventions with no immediate benefit are often raised against sham control of interventional procedures(106,113). However, recent sham-controlled surgical trials show that it is possible to obtain funding, patients are willing to participate and the sham arm is safer than the active arm(102,111). At the same time, increasing awareness is given to the fact that surgical interventions can also can be harmful e.g. causing nerve damage and complications, which can lead to chronic neuropathic pain conditions(28). On the other hand, although minimal invasive surgery in PACP may make it possible to include a sham control group in future trials, it will still be a challenge to get ethical approval with the current techniques. In conclusion, there is a push for sham-controlled trials to determine benefit versus harm of interventional procedures(114), and in clinical practice there is an increasing awareness of how placebo-related factors, such as patients' expectations, can be targeted to improve the overall outcome of clinical treatments(115).

b) Balancing benefit and harm

Question 11: Should the balance between benefits and harms of an intervention be used to optimise the outcome in studies of patients with PACP?
Answer: We advise that a careful consideration of both benefits and harms is used in the evaluation of interventional studies of patients with PACP.
Quality assessment: Moderate
Recommendation: Conditional
Agreement: Strong

Comments: In clinical practice, the effects of a given treatment are difficult to evaluate if e.g., intake of the analgesic varies freely depending on pain intensity, which is in inverse proportion to dose (i.e., the more analgesic taken the less pain). Attempts have been made to develop composite scores taking pain intensity and analgesic dose into consideration to improve outcome assessment(116), but no method has received widespread acceptance and their validity remains unknown(82). For example, instruments such as the pain management index has been developed to evaluate pain intensity and use of analgesics in a combined score in cancer pain(117), and the method was recently used to access the degree of undertreatment in patients with pancreas cancer(118). However, as always in chronic pain, the period of observation is critically important. The balance between benefit and harm may shift over time and this shall be taken into consideration. Side-effects are also important to take into consideration and a careful evaluation of the efficacy of analgesics in conjunction with adverse effects is an integral part of assessment of treatments for PACP. Only treatments with proven beneficial effects and acceptable harms are likely to make a clinically relevant benefit for the patients. However, the evaluation of benefit vs. harm is not straightforward and several approaches have been used for this task. For example, the utility function was developed to provide a method for integrating benefit and harm of a medical treatment using one single measure. This method was originally based on population based pharmacokinetic–pharmacodynamic models, which made it difficult to use in a clinical setting (119,120).

Consequently, a pragmatic utility function was constructed based on clinical measurements of benefit and harm, but without making assumptions about the underlying pharmacokinetics (121). This model typically includes two binary clinical outcomes, for example the proportion of patients with pain relief and the proportion of patients with clinically relevant side effect. These parameters can then be summarized into a benefit and harm graph showing the utility function over time for a given treatment (figure 4). This approach has proven feasible for the evaluation of pregabalin efficacy in the context of PACP, where an overall harmful effect was seen during the initial titration period, while a beneficial effect was observed after approximately two weeks (121). Such information can be used to inform patients prior to treatment initiation and thus to enhance compliance. Also, utility functions may be valuable for the evaluation of invasive procedures, but have not yet been employed for this purpose.

----------Figure 4 near here----------

<u>Question 12:</u> Should the Patient Global Impression of Change (PGIC) questionnaire be used to assess the balance between benefits and harms of pain-relieving treatments in studies of PACP?

Answer: We suggest the use of the PGIC questionnaire to assess the balance between benefits and harms of pain-relieving treatments in studies of patients with PACP, but validation studies are needed.

Quality assessment: Low

Recommendation: Weak

Agreement: Strong

Comments: In many patients the side effects of a pain relieving treatment outbalance the beneficial effects, and in such cases the net effect is negative although a positive effect may be seen when unidimensional pain assessment instruments are used for evaluation. The Patient Global Impression of Change (PGIC) may be used for an integrated evaluation of benefits and harms of new pain relieving treatments (122). This measure reflects a patient's belief about the efficacy of treatment using a 7-point scale depicting the patient's rating of overall change in wellbeing during the treatment period. Though often used, there are few studies validating the PGIC. Scott and McCracken undertook a validation study and their results imply that in addition to the PGIC, domain-specific items should be considered in treatment trials(123). The PGIC has been used as an outcome measure in relation to PACP(15), but has not been formally validated against other measures of benefit vs. harm such as the utility function(123).

c) Pancreas specific factors in pain

<u>Question 13:</u> Are there any unique features of PACP that should be included in pain assessment questionnaires?

Answer: We suggest that a number of unique features of PACP (including pain localization, descriptors and triggers) are integrated into pain assessment questionnaires.
Quality assessment: Moderate
Recommendation: Conditional
Agreement: Strong

Comments: The presentation of pain in patients with CP is variable and dependent on various disease and patient related factors. Nonetheless, the typical pain associated with CP is localized in the upper abdomen and radiates to the back. Patients classically describe their pain as a dull, sharp or nagging sensation and characteristically it worsens after meals (postprandial pain). In some cases, pain may be relieved by fasting and avoidance of fatty food content and consequently many patients lose weight due to pain induced anorexia (16). Pancreatic enzyme intake can have a mild, ameliorating effect on PACP and diabetic status, especially if complicated by neuropathy, can also impact pain sensation and can be added to assessment. Intensity and frequency may vary, but the pain itself is well known to the patient. However if a new complication develops such as biliary obstruction with cholangitis, patients may recognise the difference in the nature of pain. As such patient perception of the pain is the key element. Generic pain questionnaires do not capture these unique features of CP related pain and development and validation of questionnaires specifically designed for use in patient with CP has been identified as a need in the field (26,28).

<u>Question 14:</u> Should specific patient and disease related domains be considered in the design of future clinical trials of treatment for patients with PACP?
Answer: We advise that a number of patient and disease related parameters (including patterns of smoking and alcohol consumption, underlying genetics and obstruction, pain characteristics, opioid use and presence of comorbidities) are considered in the design of future clinical trials of treatment for patients with PACP.
Quality assessment: Moderate
Recommendation: Conditional
Agreement: Strong

Comments: Sustained alcohol consumption and smoking are associated with increased pain prevalence and alcohol abstinence and smoking cessation improve the effect of pancreatic surgery (7,8,124). Likewise, patients with hereditary or idiopathic CP, as opposed to alcoholic CP, have improved outcomes from TPIAT (125). However, in a study investigating outcome following resection or decompressive procedures, patients with alcoholic CP had the most favourable outcome (126). These findings are contradictional and further studies are needed to clarify the effects of alcohol and smoking on outcome in the context of painful CP and treatment outcome.
Progression and duration of pain may impact on the outcomes from particularly invasive treatments. Hence, observational studies of endoscopic and surgical therapy have shown improved outcomes when performed during the early phase of CP. In a retrospective multicentre study, surgery within 3 years of pain onset, 5 or fewer endoscopic procedures and avoidance of opioids were all reported as

independent predictors of favourable surgical outcome (127). Recently, these findings were established in a trial randomizing patient to early surgery (within 6 weeks) or conventional pain management (pain medication → endoscopic therapy → surgery) (ESCAPE trial) (128). A favourable outcome was reported in the early surgery group although there was no difference in the overall HRQOL of patients. In contrast to surgery the effect of pain medication does not seem to be dependent on duration of pain, but further studies are needed to clarify this (129).
Another important parameter to consider is pain pattern (intermittent vs constant pain). Hence, patients with constant pain have significantly worse quality of life, greater disability, increased hospitalization rates, higher pain intensity and more night pain (8,12,130). Importantly, constant pain is a predictor of failed surgical treatment for painful CP, while intermittent pain associated with recurrent acute pancreatitis is a positive predictor for TPIAT outcome (131). These findings are further supported by studies in patients with other painful conditions, where a constant pain pattern was also associated with a worse treatment outcome (132). The mechanisms responsible for these observations are likely related to neuroplasticity of central nervous pathways (14). Accordingly, in a recent study it was shown that patients with evidence of sensitization of central pain pathways, as documented by QST, were characterized by a higher prevalence of constant pain(133).
Opioid use is associated with increased hospitalization rates and is a predictor of poor surgical outcome (11,127). On an individual patient level, however, it is difficult to determine whether opioids worsen the response to treatment per se or is simply a surrogate marker of severe pain. Patients on opioid based pain medication are generally those with more severe pain and lower quality of life, and as such are more likely to be refractory to treatment. However, in some patients opioids can interfere with pain processing and worsen hyperalgesia (opioid induced hyperalgesia)(134).
Cost drivers may also be taken into consideration as a disease related domain in studies of PACP, and some attempt have been done(135).
Imaging is widely used for assessment of patients with CP and evidence of pancreatic duct obstruction is the primary indication for invasive therapies (28). However, pain has been shown to poorly correlate with morphologic changes of CP and increasing data show that pain in most patients is a result of a complex interplay between pancreatic inflammation and pancreatic duct obstruction, nerve damage and alterations in central pain pathways (14,17,18).
Finally, a number of additional parameters including depression and anxiety, pain catastrophizing, coping mechanisms, social support, and sleep deprivation may also be important although less well studied in CP (16,49,136). Of cause only a subsection of such measures can be used as too many questions will invariably be exhausting to fill in and result in unreliable data. The underpinning principle is that the patient shall be assessed, not just the pain, and an attempt to fully understand the patient situation will include many of the parameters mentioned above.

d) Pain associated with chronic pancreatitis in children

<u>Question 15:</u> Can adult pain assessment instruments be used in children with PACP?

Answer: Although adult pain assessment instruments (including QST) can be used in children with PACP, we suggest to avoid uncritical application and conduct validation studies in children.
Quality assessment: Low
Recommendation: Conditional
Agreement: Strong

Comments: Children comprise a unique subgroup of patients with CP. In children, recurrent acute pancreatitis and CP are largely driven by underlying genetic risk factors, and unlike in adults, alcohol and smoking are rarely contributors to disease(137–139). The INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search of a CuRE) registry for children with pancreatitis indicates that about half of children with recurrent acute pancreatitis (RAP) and three quarters of those with CP have an identifiable genetic risk factor for disease, usually involved in regulation of trypsin or ductal bicarbonate secretion(138).
For children in particular, RAP and CP represent an overlapping spectrum of disease; the majority of children with CP also have diagnosed RAP (84%). Episodic intermittent pain is reported for more often than chronic pain. Chronic pain is present in about 33% of children with RAP and 41% of children with CP, often with mild to moderate chronic pain with superimposed episodic severe pain(138). Thus, in considering the assessment of PACP in children specifically, in most cases one must consider both the visceral pain arising from the acute inflammation of AP and the more complex mechanisms mediating chronic pain (see section acute vs chronic pain assessment). Guidelines for management of paediatric pancreatitis have included assessment parameters(140), and a position paper that outline the different recommendations for medical treatment of children with CP was recently published, and includes recommendations for pain assessment and management(141). However, many recommendations used data from adult patients as limited evidence has been published in the paediatric literature.

Assessment of pain in children vs. adults must consider the age-appropriateness of assessments, whether assessments are completed by the child or parent, and the unique features of childhood including neurodevelopment, schooling, and family dynamics(142). In studies of PACP in children to date, assessments have considered the degree of pain, nature of pain (episodic/chronic), interference with function, and impact on emotional health and quality of life (Table 5)(143–148). PACP may be further complicated by the interaction between child and parent, but the impact of family dynamics have, to date, been less studied in PACP. To some degree, pain assessment issues often relate to developmental and cognitive functioning. For example, young babies cannot describe their pain but neither can adults with advanced dementia who are non-verbal. In these instances, we rely on observed behaviours such as facial expressions, posturing etc. There are a number of scales in use(149). Similarly, a variety of strategies are recommended when conducting pain assessments in non-communicative adult palliative care patients(150).
Little is yet known about the role of central or peripheral sensitization in PACP in children, as sensitization assessments in CP to date have all focused on adult populations. However, as outlined in the section “Pain assessment in general”, variability in clinical presentation and underlying pain mechanisms is likely greater between patients than between different pain syndromes. This is

especially the case when central nervous sensitization and structural reorganization is firmly established and pain becomes maladaptive, self-perpetuating and independent of the initial nociceptive drive. Methods such as QST may be used in to explore the degree of peripheral and central sensitization in children with PACP (see below), and future studies in this field are highly needed.

----------Table 5 near here----------

In the largest series, INSPPIRE-2, which has enrolled >500 children to date, pain severity is assessed by patient/family self-report using a Faces Pain Scale, which is validated down to age 4 years(143). Pain characteristics collected include self-report of pain pattern (constant/intermittent), frequency, and duration. Impact of pain on life and daily function is collected by number of emergency department visits, hospitalizations, and interference with school attendance(143). Heath-related quality of life is collected by the Child Health Questionnaire Parent Form (CHQ-50) completed by parents for children 5-18 years, and children 10 -18 years of age additionally complete the Child Health Questionnaire Checklist (CHQ-87)(143). Impact on mental health is assessed by the Child Behavioral Checklist (CBCL) completed by parents, and for children age 11-18 years additionally by the Youth Self Report Form (YSR/11-18)(143). A sub-study nested under INSPPIRE-2 is a clinical trial of web-based cognitive behavioural therapy is additionally assessing abdominal pain symptomatology using a parent and child Abdominal Pain Index, the Child Activity Limitations Interview-9 (CALI-9) for disability associated with pain, a paediatric quality of life assessment (PedsQL) and various instruments for mental health or emotional impact including PROMIS scales for emotional distress and the Beth Adolescent Pain-Parental Impact Questionnaire (BAP-PIQ), which assesses family functioning and emotional impact(148).

Other studies in the medical literature evaluating chronic pain in pediatric pancreatitis are mainly focused on efficacy of surgical interventions, largely total pancreatectomy with islet autotransplant and rarely other pancreatic surgeries(145,146,151–154). In these cohorts, pain assessments have varied from simple chart review, to prospective collection of patient reported outcomes. Where formal assessments are collected in a planned, prospective manner, these have similarly included assessments of pain severity and characteristics, with the additional assessment of patient or parent perception of pain improvement after surgery. Health related quality of life has been collected by use of Short Form (SF)-36, SF-12, or SF-10(146,147,151). The PROMIS pain interference scale is currently being used to assess functional interference from pain in children enrolled in the ongoing POST study, along with assessment of mental health by the PROMIS paediatric depression and paediatric anxiety scales(147). Thus, in summary, assessing PACP in children overlaps with adult assessments in the dimensions measured including pain features, pain interference, health related quality of life (HRQOL), and emotional distress, and some of the more specific instruments utilized, but assessments in children must also consider measures that are childhood specific and collection of data by both parents and children.

<u>Question 16:</u> Does the pain system mature during childhood in children with PACP?
Answer: We suggest that neurodevelopment is considered in the assessment of pain, as the pain system matures during childhood and responses may depend on developmental stage.
Quality assessment: Low
Recommendation: Conditional
Agreement: Strong

Comments: It is not clear what impact early pain and maturation of the pain system may have on development of PACP. For some children with CP, disease onset may occur very early in life, even within the first few years after birth(137). Pain pathways in early life are not simply a modified version of adult pathways(155). Hence, neurodevelopment must be considered in the assessment of pain, as children may understand and respond differently to pain depending on developmental stage. What is less clear is what impact early pain and maturation of the pain system may have on development of chronic pain associated with pancreatitis. Research in the impact of early pain experiences has mainly focused on premature infants in the neonatal intensive care unit(156), with very little known about repeated or chronic pain during toddler or early childhood years as is experienced by children with CP. Notably, children with CP who have a total pancreatectomy with islet autotransplant in early childhood (age 3- 8 years) seem to experience more complete pain relief, with little to no chronic opioid use and fewer chronic pain syndromes than described in their older adolescents and adults counterparts after surgery. This suggests that resolution of localized visceral pain from pancreatic inflammation at an early age may be sufficient to minimize sensitization, or that neuro-regeneration is sufficient in early childhood to allow for better restoration of normal pain signalling once the localized disease is treated(152). Limited QST in healthy children without pain have demonstrated *increased* sensitivity to heat pain and mechanical pain stimuli at age 6-8 years compared to older age groups, suggesting a possible maturation of the pain system occurring before age 9 years in normal development(157,158). More detailed research on the mechanisms underlying pain, distinguishing visceral pain versus peripheral or central sensitization in children with CP will be needed to better understand the role of neurodevelopment in PACP.

<u>Question 17</u>: Should QST be applied to children with PACP?
Answer: We advise that QST require further optimization and validation before they are used in children with PACP.
Quality assessment: Moderate
Recommendation: Strong
Agreement: Strong

Comments: QST applied to adults with PACP show a significant subset of adults with segmental or central sensitization contributing to chronic pain syndrome, as discussed in greater detail elsewhere in this paper(159,160). Appropriately understanding of neuropathic contributions to pain in patients

with PACP is important because mechanisms of pain may impact which management strategies are most likely to succeed in reducing pain symptoms and pain-associated disability(85,161). To date, QST has not been directly applied to children with PACP. However, a review of the literature suggests that it would be feasible to do so.

QST has been applied in healthy children age 6 to 18 years using both thermal (hot/cold) and mechanical (pinprick/pressure) stimuli with a high degree of feasibility of implementation. Normative values appear to differ by age and, more variably, by sex and so establishing an appropriate age and sex-matched comparator cohort needs to be considered(157,158,162). While conditioned pain modulation was not included in these studies in healthy children, it has been applied to adolescents with scoliosis and chronic back pain(163). Various protocols involving QST with thermal stimuli, mechanical stimuli, and /or conditioned pain modulation have been used to assess for dysfunctional pain modulation in children with conditions associated with (mainly) non-visceral pain including sickle cell disease, neuromuscular disease, and juvenile idiopathic arthritis(163–167). Research application of QST in children will be needed to understand risk for sensitization in paediatric pancreatitis.

e) Acute vs. chronic pain assessment

Multiple mechanisms are involved in the pathogenesis of *acute visceral pain* such as that associated with acute pancreatitis. These include increased pressure in the pancreatic duct, activation of inflammatory pathways, ischaemia and tissue necrosis of the pancreas and peripancreatic fat. Increased tissue pressure from inflammatory oedema may also lead to activation of mechanoreceptive nerve endings(136). In the initial stage the pain associated with acute pancreatitis is often relatively diffuse in the upper abdomen and accompanied by autonomic symptoms such as nausea and sweating. The inflammation of peritoneum and injury to adjacent organs (including intestinal ileus, necrosis and perforation) can lead to changes in the characteristics of pain over time (2). Although PACP is classically located to the epigastrium with or without radiation to the back, it can have atypical localisation with referred pain to remote somatic structures (e.g. muscle and skin) (168). For example a recent review of 36 cases reported acute pancreatitis masquerading as myocardial infarction with chest pain and electrocardiogram mimicking ST-elevation myocardial infarction(169). Cross-organ sensitization is another complex form of hypersensitivity whereby acute pancreatitis may manifest as symptoms from another organ. This is probably explained by several mechanisms, among them convergence of afferents from pancreas and another organ on the same second-order neuron in the central nervous system(170) (figure 5). In summary, the acute pain associated with pancreatitis can vary a lot depending on the predominant disease mechanisms, and can change over time, with complications and involvement of other organs. For details about gastrointestinal pain pathogenesis and symptoms see(136).

----------Figure 5 near here----------

<u>Question 18</u>: Do the differences in the underlying pain mechanisms in acute and chronic pancreatitis require a different approach to pain assessment?
Answer: We recommend that pain assessment instruments should take account of different pain mechanisms in acute and chronic pancreatitis, although some aspects will be common to both.
Quality assessment: High
Recommendation: Strong
Agreement: Strong

Comments: Assessment of acute pain is more straightforward than chronic pain, as acute pain is a short lived experience usually with minimal impact on long-term social functioning etc. Typically acute pain intensity is measured on unidimensional scales such as numeric rating scales or visual analogue scales, the former preferred in age-mixed populations(171). However, it has been argued that questionnaires should also include interference with e.g., sleep and emotional functioning(172). Assessment of pain during movements is also used, and is likely more relevant than pain at rest(173). During trials of analgesic treatment of acute pancreatitis, other measures such as dose of rescue analgesics and duration of pain relief can also be used(174). Of note, acute and chronic pain are very different, and chronic pain level of 3 may be worse that an acute pain level of 10 as the discomfort of pain depends on the patients perception of the origin and potential duration of the pain – can they "tough it out", or is it only moderate but hopeless? However, there is an overlap to assessment of chronic pain, see section "Pain assessment instruments in general" and the considerations below, but the duration of acute pain shall also be taken into consideration as it will share many mechanisms with chronic pain the longer it last.

<u>Question 19:</u> Can pain assessment instruments for PACP be used for patients with recurrent acute pancreatitis and acute-on-chronic pancreatitis?
Answer: We recommend that elements from pain assessment instruments used for both acute and chronic pancreatitis are considered in the evaluation of patients with recurrent acute pancreatitis and acute-on-chronic pancreatitis, but these instruments will require optimization and validation in these settings.
Quality assessment: Moderate
Recommendation: Conditional
Agreement: Strong

Comments: Although there is major overlap, it is a common mistake to not discriminate between acute and chronic pain mechanisms, and this can lead to suboptimal assessment and treatment of PACP. Although 'acute on chronic' pancreatitis can be considered a transition condition, most patients presenting with PACP have end-stage disease and chronic (> 3 months) pain(175). In contrast to the pathophysiological mechanisms underpinning acute visceral pain, patients with CP have increasing fibrosis, and in later stages inflammatory cells are usually sparse(1). This is in sharp contrast to acute pancreatitis with oedema, inflammatory cell infiltrate, ischaemia and necrosis. One key mechanism in PACP include damage to local pancreatic nerves along with neural sensitization

of the peripheral and central nervous systems (14). With this sensitization and reorganization of central pain pathways pain becomes maladaptive, self-perpetuating and relatively independent of the initial nociceptive drive (figure 5). These changes are not restricted to PACP, and are present in most conditions associated with chronic pain (60). In some patients, secondary complications may dominate or confound the presentation of pain. For example, fibrosis and inflammation can change the perfusion of neighbouring organs, alter visceral reflexes and hormonal control leading to complications such as peptic ulceration, motility disorders, small intestinal bacterial overgrowth and intestinal/organ ischaemia, all of which can increase and alter pain(1,16,176). Therefore, it can be considered to include extra-pancreatic sites of pain in questionnaires where such complications are explored. Chronic pain is also associated, to a much greater degree, with the affective and cognitive complications associated with pain. This means that the assessment of PACP necessarily conforms to a high degree with approach used in other diseases, also dominated by chronic pain. Hence, PACP assessment and its impact on physical, emotional, and social functions requires multidimensional qualitative tools and health-related quality of life instruments (173) that are not needed in acute and acute on CP, see section "Pain instruments in general". On the other hand, taking the lack of evidence into consideration, elements from chronic pain assessment such as interference score and impact on sleep can be addressed when evaluating acute on CP. It will also be recommended to assess the duration of pain and pain-free periods in these patients.

Quality of life, mental health and quantitative sensory testing

Quality of life and mental health in PACP

<u>Question 20</u>: Should instruments to evaluate quality of life and mental health be used in patients with PACP?
Answer: We advise that instruments to evaluate quality of life and mental health are used as part of the assessment of patients with PACP
Quality assessment: Moderate
Recommendation: Strong
Agreement: Strong

Comments: While the cardinal clinical feature of CP is pain, severe and persistent pain may lead to downstream consequences including impaired HRQOL and emotional distress, and many questionnaires were developed and validated for this (130,177–180). HRQOL measures are frequently incorporated into the assessment of PACP and medical or surgical therapies to treat CP(63,128,147,181–186), see also section "Pain instruments in general". Standardized measures of HRQOL generally incorporate dimensions of both physical and mental/emotional function. While more specific measures of depression and anxiety are less commonly reported in studies of CP, limited data are available that suggest a high risk for depression and anxiety, and this should be considered when designing studies for PACP(179).

When considering measures of HRQOL to incorporate into CP research, available instruments can be generally divided into two categories: (1) general measures of HRQOL which are not specific for CP or pancreas disease; and (2) measures specific for pancreas disease or pancreatitis. Perhaps the most widely used instruments in published CP research to date have been the generic measures of Short Form-36 (SF-36) or SF-12 and the European Organization for Research and Treatment of Cancer QOL Questionnaire Core questions 30 (EORTC QLQ-C30). Although these instruments are not designed specifically for pancreatic disease, and therefore in theory may lack specificity for disease-specific impact on HRQOL, published studies using either measure consistently show impairment in HRQOL compared to a healthy control population or established population normative values(130,181,187). Many surgical and some medical treatment studies using either instrument have also demonstrated improvements in HRQOL with established CP therapies, suggesting that these assessments are valid for measuring treatment responses(63,128,184,188–190). Hence, the International Study Group for Pancreatic Surgery document on reporting standards for all CP surgical procedures, voted to discontinue the Izbicki pain questionnaire and rely on HRQOL measures(191). With regards to pancreas-specific measures, the EORTC PAN26, which was developed for outcomes research in pancreatic cancer, has been used widely in pancreas surgery outcomes research, as a companion tool to QLQ-C30. While not designed for use in CP, previous research has established this tool as a valid instrument for CP research(192). More recently, to address the lack of a *pancreatitis-specific* instrument, the pancreatitis quality of life instrument (PANQOLI) was developed, validated, and is beginning to be incorporated in the design of CP treatment studies(177,193–195). This 18 item-scale correlates well with generic HRQOL measures and contains a total of 4 subscales: physical function, role function, emotional function, and self-worth.

Impaired HRQOL is correlated with pain symptomatology. Greater pain severity or pain intensity in patients with PACP have corresponded with lower global health scores and reduced subscale scores with the EORTC QLQ-C30 and PAN26 and lower component summary scores on SF-12(12,187,196). Data from over 1,000 patients with CP in the North American Pancreatitis-2 Study (NAPS2) found that constant pain, pain-related unemployment or disability, smoking, or concurrent comorbidities were associated with lower HRQOL by SF-12(130). A recent study showed that lowered HRQOL was directly associated with constant pain and opioid based pain treatment, confirming the relevance of this measure in pain research(197). In a different cohort of 1,146 patients with prior history of duodenum preserving pancreatic head resection, those patients with a successful outcome defined by relief of pancreatic pain also had higher HRQOL by QLQ-C30(198).

In CP, the combination of chronic illness, recurrent or chronic pain, and social isolation may all present risk for depression and anxiety. While studies of psychiatric comorbidities are relatively limited in CP, particularly in contrast to the abundance of literature on pain and HRQOL, available data suggest a high risk for depression. In 692 patients with non-alcoholic CP assessed for depression using the Center for Epidemiologic Studies 10-item Depression Scale (CESD), 52% scored above the clinical cut-off for depression symptomatology(179). Those patients who met scoring criteria for depression also had a higher pain score and low HRQOL by SF-12 component summary scores. A separate, small study of CP patients identified depression and anxiety, using the HADS, more often in smokers than non-smokers(194). A recent study in 171 patients with CP

showed that anxiety and depression were present in about 45 and 40% of patients(9). The psychiatric comorbidities were associated with reduced global health scores and functional subscales as well as higher symptom burden. In this study anxiety was likely mediated via pain, whereas depression was independently associated to reduced global health scores (ref). Specific assessments of anxiety are otherwise largely lacking, though research on patients requiring opioid treatment for chronic pain in general suggests a high rate of both depression and anxiety in the chronic pain population, with about half of chronic pain patients carrying either diagnosis(199). Thus, as CP research advances, consideration of more specific assessments for depression and anxiety is warranted.

Quantitative sensory testing

<u>Question 21</u>: Can QST be used to characterize PACP?
Answer: We recommend that QST, although still a research tool, is used in specialist settings to phenotype individual patients
Quality assessment: Moderate
Recommendation: Strong
Agreement: Strong

Comments: Abnormalities in the sensory system and mechanisms underlying pathologic pain disorders can be studied with QST(200,201). The rationale for QST is that different neural pathways and networks are investigated with standardized stimulation of somatic or visceral tissue. The response is then quantified with psychophysical and/or objective methods (such as electroencephalography, nociceptive reflexes, autonomic responses and imaging) that reflect the state of the nociceptive system in a standardized and reproducible way. A stimulus-response curve, characterizing the subjects' state of pain processing, can be constructed by increasing the stimulus intensity gradually until the subject reaches a predefined sensory threshold (e.g. pain detection or tolerance threshold). Inhibition of pain by descending pain modulation is a response to a noxious stimulus inhibited by another noxious stimulus from the central nervous system ("pain inhibits pain"). The conditioned pain modulation paradigm (CPM) can measure this response. During CPM a test stimulation is applied (e.g. electrical or thermal), followed by a conditioning stimulus which inhibits pain (e.g. cold pressor test via ice water bucket immersion at the contralateral arm/foot), and then again, the test stimulation is applied. The difference between the two test stimuli is the effect of descending pain modulation(202). When changes in the central nervous system due to chronic pain are present, descending modulatory mechanisms often fail, resulting in a further increase in pain(203,204). Interesting, a recent study showed that QST characterizes pain phenotypes independently of psychiatric comorbidity, indicating that this may be a robust measure of the "nociceptive component" in clinical pain(133). There is, however, a need for prospective large scale studies before QST can be recommended as a tool for ordinary clinical practice.

<u>Question 22</u>: Are there different recommendations for bedside and invasive QST testing of patients with PACP?

Answer: We recommend using non-invasive somatic stimuli with QST for phenotyping each individual patient's nociceptive profile, instead of invasive visceral stimuli.

Quality assessment: Moderate

Recommendation: Conditional

Agreement: Strong

Comments: In patients with gastrointestinal diseases, including PACP, QST with stimulation of the upper or lower gastrointestinal tract has been used to characterize neuroplastic changes in central pain pathways(205). However, visceral noxious stimuli are unpleasant to the patient and difficult to use in a clinical setting. Due to convergence between visceral afferents from the pancreas and somatic afferents from the upper abdominal area (T10 dermatome) at the same neuronal structures in the spinal cord, QST of the skin and underlying somatic structures can be used to assess whether or not the central pain pathways are sensitised by nociceptive input from the pancreas. Hence, by measuring the differences between the affected site (dermatome T10 for pain associated with CP) and anatomical sites more distant, a differentiation can be made between signs of segmental (spinal) and widespread (supraspinal) central sensitization (figure 6).

----------Figure 6 near here----------

Multiple clinical studies in patients with CP have used QST to characterize pain and changes in pain processing(204,206–208). Segmental and widespread hyperalgesia, together with increased areas of referred pain, was consistently found across studies. For example, increased areas of referred pain to electrical stimulation of the upper gastrointestinal tract (oesophagus, stomach and duodenum) was reported in patients with PACP compared to control subjects. Other studies reported decreased pain thresholds to visceral stimulation of the rectosigmoid as well as somatic stimulation of muscle and bone. These findings reflect a generalized hyperalgesic state, which imply the presence of central sensitization, and seem to be linked to disease severity as documented by the M-ANNHEIM classification(204,209,210).

Failure of inhibitory mechanisms from the central nervous system on pain like descending pain modulation have also been observed in different CP studies. Descending modulatory mechanisms often fail due to the presence of central sensitization, leading to a decreased activity in the inhibitory pathway of the spinal cord and an increase in the faciliatory pathway, resulting in more pain(201,203,204,206,207).

Multiple studies have used somatic (i.e. skin and muscle) and visceral (i.e. oesophageal or duodenal) stimuli during QST in patients with PACP. Overall these studies show comparable results in terms of hyperalgesia to the applied stimuli(13,14,19,86,161,203,206,210–214). Notwithstanding the similarities in findings across QST studies based on somatic and visceral stimuli, an adequately powered head-to-head comparison between visceral and somatic stimuli has

never been performed in patients with CP. However, when somatic stimuli are compared to visceral stimuli the burden for patients is much lower with somatic stimuli, and it is easier to apply, especially in a bedside or outpatient situation. Also, less skills and advanced equipment are needed for somatic stimuli used during QST(203).

Question 23: Can QST be used to predict response to treatment in patients with PACP?
Answer: We advise that QST, although still a research tool, can be used in expert settings to predict response to treatment in patients with PACP.
Quality assessment: Moderate
Recommendation: Weak
Agreement: Strong

Comments: QST has also been used to study the effects of pain treatment on pain processing in relation to its clinical effect. S-ketamine infusion, a non-competitive NMDA receptor antagonist whose activity is related to central sensitization, resulted in a short-lasting increase in pain pressure thresholds, without a reduction in clinical pain in patients with PACP(207). In another study, pregabalin, a gabapentinoid that can be used to treat neuropathic pain, showed significant analgesia in patients with PACP, which was associated with a moderate anti-hyperalgesic effect. Interestingly, patients treated with placebo in this study showed a decrease in their clinical pain scores without any changes in their pain thresholds measured by QST, reflecting that QST may be a less biased measure of the nociceptive process than subjective pain assessment (86,211). However, it should be noted that studies in patients with pain due to somatic diseases, the placebo effect was shown to affect QST as well(215,216). In a sub-study of the same patients with PACP, it was shown that responders to pregabalin had more segmental hyperalgesia in the pancreatic dermatome reflecting nervous system sensitization at the spinal level(85). Patients with effect of the medication also had improved conditioned pain modulation(86).
QST was also used in patients with PACP undergoing pain-relieving pancreatic surgery. Patients with a poor pain outcome after surgery showed more central sensitization and less effective descending pain modulation compared to patients with a good pain outcome(212). The relation between disease progression in patients with PACP and pain is not well understood. In one exploratory study, a relationship was found between the severity of the disease and pain thresholds (more hyperalgesia, evident as lower pain thresholds at more severe disease stages)(204).
More recently a QST paradigm specifically developed for characterisation of pain processing in CP was developed (P-QST) including normative reference values (figure 5)(159). This method may be used to predict outcome of for example invasive (endoscopic treatment or surgery) and thus to tailor management on an individual patient level, and preliminary data shows promising results(217).

<u>Question 24:</u> Should QST be part of the investigational armamentarium in randomized trials of patients with PACP?
Answer: We recommend that QST is used in randomized trials to define the nociceptive profile of patients with PACP to better understand and predict treatment effects
Quality assessment: Moderate
Recommendation: Conditional
Agreement: Strong

Comments: Pain in CP is complex due to its temporal nature, variability in severity and poor correlation with morphological changes of the pancreas. The majority of clinical studies on pain in CP do not capture the complexity of visceral pain and do not look at pain mechanisms. Therefore, additional methods like QST can be helpful for characterizing of sensory processing and provides a means for phenotyping nociceptive profile on an individual patient level. Recent studies have shown that the nociceptive profile assessed with QST differs between patients(159), thus strengthening the need for QST to assess nociception. Identification of such nociceptive phenotypes can potentially allow for individualized treatment approaches that will possibly lead to more effective pain management and improved patient outcomes(203,214). However, QST is still a research tool, and studies shall, if possible, be done in conjunction with the consortium for pancreatic QST to ensure homogeneity between trials.

Chronic pancreatitis specific pain questionnaires

Generic pain assessment questionnaires or tools are frequently used in studies of PACP. An overview of studies in PACP using these tools are provided in Table 6. The general pain assessment tools were developed for other diseases and most have not been validated in CP patients (for details see section “Pain assessment instruments in general”). On the other hand, CP-specific pain assessment tools do not cover all aspects of pain. In general questionnaires can be grouped as:

1. unidimensional tools that assess one aspect of pain, with the visual analogue scale (VAS) being the most commonly used
2. bidimensional tools that assess two aspects of pain
3. multidimensional tools that assess multiple aspects of pain, and
4. tools that assess mental and emotional aspects of pain, often together with quality of life assessment.

----------Table 6 near here----------

Of all the general pain assessment tools mentioned in Table 6, only the BPI, the Short Form-12 Health Survey (SF-12), and the Medical Outcomes Study Short Form-36 Health Survey (SF-36) are validated in PACP and the Health Surveys are measuring the consequences to chronic pain rather

than pain per se(12,26,235). The CP-specific pain assessment tools are shown in Table 7(26). The Izbicki pain score is used most often in clinical studies of CP patients, and focuses on four common aspects of pain including intensity, frequency, analgesic use and inability to work(57). The average of these four sub-scores makes the final pain score, where a higher score being associated with worse pain. The All India Institute of Medical Sciences (AIIMS) also developed a continuous pain score (0-12) for PACP and included frequency of pain and treatment severity, but has until now only been used in the local settings(59,236,237). The Ammann, Type A-E, Group 1-3 pain patterns and the COMPAT were all developed to classify the common pain patterns in CP(20,238–240). These pain patterns are quite widely used and capture constant, intermittent and mixed pain patterns with varying intensities. CP specific quality of life tools are the Quality of Life Questionnaire-Pancreatic Modification (QLQ-PAN26), the European Organisation for Research and Treatment of Cancer QOL questionnaire (EORTC QLQ-C30) and Pancreas Quality of Life Instrument (PANQOLI), and they have also been validated in PACP(192,193).

----------Table 7 near here----------

<u>Question 25</u>: Are there recommendations about which questionnaire should be used to assess patients with PACP?
Answer*:* We suggest that multiple pain assessment tools (including questionnaires) are used to assess patients with PACP, as validated instruments are not yet tested in clinical trials
Quality assessment: Low
Recommendation: Weak
Agreement: Strong

Comments: As can be seen in Table 6, most studies in PACP, including randomized controlled trials, used unidimensional pain assessment tools. As described by Teo et al. there was striking lack of association between the characteristics of the study (e.g. type of intervention, study design, patient population and study duration) and the general pain assessment tools used in these studies(26).

In Table 8 the different aspects of pain are shown for the general multidimensional tools and CP-specific tools. These tools are highly selective in regards to which aspects of pain are assessed and they also differ in the assessment of the character and burden of PACP. It is also worth noting that most of the pain assessment tools focus on the somatic or bodily pain experiences, with the emotional/mental aspects of pain and quality of life underreported. Strikingly, the duration of pain (referring to length of symptomatic disease, and an important predictor of treatment success) or the impact of pain on mental status and daily function are lacking in many pain assessment tools(26). As can be seen in Table 8, COMPAT is most complete in describing the different dimensions of pain in CP, but validation still needs to take place in a sufficiently large cohort of patients.

----------Table 8 near here----------

Besides COMPAT, there is no pain assessment tool that covers all aspects of pain and there is the need for improved questionnaires and tools for pain assessment. Table 9 summarizes the different recommendations for pain assessment by local and international guidelines(26). There is significant room to improve pain assessment in PACP to the benefits of both clinical care and research studies. Because of the limited literature and sparse evidence, it is not possible to make a robust recommendation as to which questionnaire or tool should be used to assess PACP (Table 10). It is therefore recommended that multiple pain assessment tools are used to evaluate the different aspects of CP pain, for primary and secondary study outcome parameters etc., see also "Conclusion section".
Employment is embedded in many of the domains recommended, and is an important core outcome from any intervention. Socio-political issues such as unemployment rates in a particular country should be taken into account when using employment rehabilitation as a key outcome metric. Any system also needs to be validated across a number of domains including language, and socio-economic status of the individual, but also the country. In middle income and low income countries and in maybe communities with a different cultural interpretation, the common understanding of an item needs to be ensured. There will be a need for region or resource-sensitive normative data as baseline, and linguistically and culturally validated versions as normative differences observed in populations are multifactorial, including language, culture (with religion playing an important role).

----------Table 9 near here----------

The criteria mentioned in table are proposed by the American Gastroenterological Association (AGA)(242) with aspects of pain from the literature(15,231,234,243), compared with recommendations from international consensus guidelines(243–246)

----------Table 10 near here----------

<u>Question 26</u>: What specific aspects of pain should be included in questionnaires for patients with PACP in contrast to general questionnaires for pain assessment?
Answer: We suggest including several specific aspects of pain in assessment of patients with PACP, including pain localization, character, provocative and relieving factors, radiation pain, as well as specific coping factors.
Quality assessment: Low
Recommendation: Weak
Agreement: Strong

Comments: No consensus exists on which aspects of questionnaires are best used to characterize PACP and its burden. A large number of pain facets are found in the literature, see also section "Pain assessment instruments in general". They can be categorized into the following groups:

1. aspects directly related to pain (i.e. location, duration, intensity and aspect, analgesic use and relieving factors)
2. psychological aspects (i.e. effect on mental health and social functioning), and
3. aspects related to quality of life (i.e. ability to work/occupation status and effect on daily activity)
4. financial hardships in terms of loss of work, additional health related costs etc.
5. domains with a cultural/social/gender/ethnicity context

Dimensions of pain within each of these groups provides a foundation for developing a pain assessment tool that is specific for CP. This was also recommended for pain assessment in general across the underlying diseases (see section "Pain assessment instruments in general")

The American Gastroenterological Association (AGA) proposed 8 different criteria for the evaluation of PACP(242), and an international consensus recommended three further aspects (Table 9) (2). However, there is no clear agreement about which dimensions of pain should be evaluated in CP, and Table 8 shows that besides COMPAT, no single pain assessment tool covers all different aspects of CP pain.

<u>Question 27:</u> Is it necessary to develop two different pancreatitis specific pain questionnaires, for the clinical and research settings?
Answer: We recommend developing and validating a multimodal pain assessment tool for patients with PACP that can be used in both the clinical and research settings, although for some research questions more comprehensive instruments may be needed
Quality assessment: Low
Recommendation: Weak
Agreement: Strong

Comments: While the setting of pain assessment does not alter the pain experience, there are practical considerations, which could necessitate different approaches to the pain questionnaires in the different circumstances. Research studies allow for more detailed exploration of issues and involve a significant investment in time and personnel. This will not translate to the typical clinical settings and some compromise must be achieved. It may be advantageous to have a relatively short questionnaire for routine clinical care where the assessment of pain intensity, the determination of whether central sensitization has occurred, and the change with time and treatment are most important in guiding management decisions. A brief questionnaire may also suffice for some research, but there is an urgent need for a validated and comprehensive pain assessment tool specific for CP that captures all the domains of pain and its holistic impact on the patient. Such a

comprehensive approach is particularly important when evaluating new pain assessment tools and treatment strategies.

Pain assessment in CP has traditionally relied on general pain assessment tools and there has been a paucity of research dedicated to the development of tools that are specific for PACP. The design of a pancreas specific pain questionnaire must incorporate both generic and specific elements/domains. The process will move from being predominantly generic to incorporate more specific aspects over time, with more research and knowledge. The questions must allow valid patient reporting of their subjective pain experience, and the questions must not themselves confound or filter the answers. The process of developing such a pancreas specific pain questionnaire will be iterative because there is no gold standard in pain assessment of patients with CP. Thus, the development of pancreas specific pain questionnaires will also need to be comprehensive at the outset (i.e. capturing many aspects of pain) before being able to remove some aspects as less important in assessing PACP, based on evidence. The COMPAT has been developed to fulfil these requirements, and is currently undergoing further validation studies. However, due to the many questions it is very time-consuming to fill in and patients may find it difficult. Therefore, the original COMPAT will likely only be useful in specific pain studies with dedicated patients and researchers. A short-form of COMPAT (SF-COMPAT) has been recently been constructed and evaluated for reliability and validity in a multicentre prospective study(92). This questionnaire will likely be useful in clinical and research settings, but will need testing in future studies.

Conclusion

Abdominal pain is the most common symptom of chronic pancreatitis, and the strongest predictor of poor quality of life. Although pain has been the focus of many experimental and clinical trials, there is no consensus on how to measure pain associated with chronic pancreatitis, and few instruments are tested for reliability and validity. This guideline has reviewed the existing questionnaires used for pain in general, assessed confounding factors and pain types as well as specific factors considered in the settings of different phenotypes, pain in children and acute pain. We also reviewed the value of quantitative sensory testing in pain assessment. Finally, a systematic approach was used to review pain assessment questionnaires in relation to chronic pancreatitis.

We conclude that assessment of pain in chronic pancreatitis can be done in many ways and depends on the research questions asked in the specific trials or clinical settings. Although some aspects of pain in chronic pancreatitis are specific for this disease, chronic pain is dominated by central sensitization irrespective of whether it originates in visceral or somatic structures, and assessments and questionnaires used in chronic pain are valid in most settings. It is therefore recommended to use core domains from chronic pain in general such as the IMMPACT guidelines for secondary outcomes, including their recommendations for clinically relevant changes and endpoints. Changes in pain severity do not necessarily track with patients' ratings of improvement and satisfaction, hence multidimensional questionnaires are recommended. Some instruments such as the Izbicki

pain score encompass several of the recommendations above including consumption of analgesics, but although widely used, it has never been systematically validated. However, as the Izbicki pain score has been used in many trials it could be added for future meta-analyses and for comparing outcomes with previous trials. Recently, a comprehensive study unravelled all different aspects of pain in chronic pancreatitis and constructed the COMPAT questionnaire. This is, however, too time consuming and comprehensive to be used in most clinical trials and the validated short version, where the most important features are preserved, will likely be more attractive.

As placebo effects are estimated to account for about 30 % of the responses in clinical trials; these always need to be taken into consideration before any firm conclusions can be drawn. Side effects from medication or endoscopical/surgical interventions shall also be considered in the assessment as they may downstage the global effect of pain management. Semi-objective measures such as quantitative sensory testing and imaging have shown promising results, but as pain is a subjective and complex sensory experience, these modalities only capture some aspects of the nociceptive processing rather than pain per se.

Although pain in patients with chronic pancreatitis has similarities with other types of chronic pain, there are still specific factors (such as postprandial pain) and phenotypic characteristics associated with this disease that shall be considered in pain assessment. In is also recommended to assess quality of life and psychiatric co-morbidity as this has major impact for pain treatment and consequences of the disease. Assessment of pain in children shall include the unique features of childhood including neurodevelopment, and family dynamics. A flowchart on how pain assessment can be done in different studies is shown in figure 7.

----------Figure 7 near here----------

It is also considered important that any pancreas specific pain questionnaire attempt to capture the result of different pain mechanisms. A mechanistic framework with relevance to both the assessment and treatment of PACP seeks to answer three questions:

1. What is the source of nociception? (i.e. visceral and/or somatic),
2. Is nociceptive transmission altered? (i.e. peripheral nerve sensitization and damage can become a source of nociceptive input in itself).
3. Is central pain processing altered? (i.e., increased responsiveness of central pain transmitting neurons and reorganisation in their network, where generalized hyperalgesia is associated with more pain through a pro-nociceptive shift in central pain modulation).

To this sort of framework, other important dimensions and consequences of PACP will need to be captured for the development of a pancreatitis specific pain questionnaire, such as the impact on physical, emotional, and social functions. It is also recognized that a pancreas specific pain questionnaire may be further modified with the advent of objective tests of pain, including biomarkers such as QST.

There are still many challenges in pain assessment and current dilemmas are outlined in Table 11. In the design of future trials of pain in chronic pancreatitis, the current guidelines will undoubtedly improve assessment of pain and make it more homogeneous and comprehensive. This will make it possible to compare the many different dimensions of pain in future reviews and meta-analysis, and improve management of the most challenging complication of chronic pancreatitis.

----------Table 1 near here----------

Figure legends

Figure 1. Flowchart illustrating the working process. PICO: Population; Intervention; Comparator; Outcome; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; GRADE: Grades of Recommendation, Assessment, Development and Evaluation. For details see text.

Figure 2. Information flow in the literature review

Figure 3. The Likert scale

Figure 4. A theoretical example of a pragmatic utility function. The graph illustrates the utility function (weighted measure of effects and side-effects) in pain treatment with tricyclic antidepressants, where it is well known that it will take some days, maybe weeks before the analgesic effect (pain intensity) exceeds the side effect profile (combination of symptoms such as sedation, dizziness, anticholinergic symptoms etc.). The grey area indicates the probability of benefit (positive values) minus the probability of harm (negative values).

Figure 5: Schematic illustration of pain mechanisms in acute and chronic pancreatitis. The acute disease (green circle) is dominated by inflammation and increased barrage via peripheral nerves leading to the spinal cord and traditional pain centres in the brain. Local complications such as paralytic ileus (2) and intestinal ischemia (3) can contribute to the clinical pain picture together with activation of local and autoimmune reflexes via splanchnic and vagal pathways (4). A proportion of patients with chronic pancreatitis have neural sensitization and structural reorganization of central pain pathways (red circles) (7) with the generation of pain which becomes maladaptive, self-perpetuating and relatively independent of the local nociceptive drive. Long-standing pain also activates brain centres involved in physical, emotional, affective and cognitive functions (8). Pain control (typical inhibitory) mechanisms descending from the brainstem are often dysfunctional as well (9). Both in acute and chronic pain from the pancreas, central convergence with somatic nerves 5) and nerves from other viscera (6) can give symptoms from remote the muscle/skin and other organs. For detail see(136). Although there is an overlap in the different mechanisms, this explains why assessment of acute and chronic pain is different.

Figure 6: Schematic illustration of the bedside method (P-QST) used for objective assessment of the pain system in patients with PACP. Due to convergence between afferents from the pancreas and those of the skin in the Th10 dermatome (abdomen and back), any increased afferent barrage from the pancreas due to peripheral sensitization (white star) may result in central sensitization of spinal cord neurons at this level as illustrated with the opaque star. This will result in a segmental lowering of the pain threshold to quantitative sensory testing (QST) of the skin and deep tissue (QST 1). If the sensitization spreads along the neuraxis (opaque star at S1 segmental level) there will also be a lowering of pain thresholds in other areas as illustrated with S1 (QST 2).
The efficacy of bulbo-spinal descending pathways (black arrow) that can gate the afferent barrage and this inhibit pain pathways are also tested indirectly, and the response to repeated pinprick stimuli at Th10 and control site reflects neuronal sensitization.

Subjective pain is, however, not only a result of nociceptive processing, but also activates brain centres dealing with affective, cognitive and evaluative processing involved in the complex sensory process (opaque stars at brain level). During chronification such components of pain may dominate the clinical picture.

Figure 7. Flowchart showing proposed methods for assessment of pain associated with chronic pancreatitis. For clinical management and in studies where pain is a secondary research topic, it is recommended to use few validated instruments together with registration of side effects. When pain is the primary research topic, assessment shall always be modified depending on the specific research questions. For experimental studies, primary endpoints will typically be advanced objective and very detailed assessment of the pain processing, although such measure can also be nested in clinical studies. In clinical studies, the age group shall be considered. Pain assessment in children shall follow the guidelines in the section "Pain associated with chronic pancreatitis in children". In adults, the approach will depend on whether pain is intermittent with little background pain, or mainly constant with relative high pain intensity. In the former cases chronification with central sensitisation etc. has likely not developed, and it is suggested to use instruments that target pain intensity with diaries and assessment of pain duration as primary endpoints. Most patients that are considered for randomized controlled trials will suffer from constant background pain (+/- acute exacerbations). Recommended primary endpoints are validated questionnaires such as either BPI or a diary with pain intensity rated on a numeric rating scale (VAS are often more difficult to use). More comprehensive outcome measures such as SF-COMPAT can also be used. As "chronification" is expected in such patients, more detailed descriptions of the pain consequences for cognition, anxiety, quality of life etc. are needed for secondary outcomes as outlined in in section "Pain assessment instruments in general". It should be emphasized that no valid questionnaires or investigations can identify whether chronification and central sensitization is present in a given patient. However, long-lasting pain and high psychological impact indicate central neuroplastic changes, and QST can be of support where available. Some researchers may prefer to use other pancreas specific questionnaires such as the Izbicki score (see section "Chronic pancreatitis specific pain questionnaires"), but these are not tested for validity, and cannot stand alone. Selection of secondary outcomes will depend on factors such as the research questions, expected compliance, and any specific characteristics for the medication/procedure. Differences in regional settings, language etc., may also influence selection of secondary endpoints, but these should always include physical and emotional domains as well as a global outcome measure.
BPI: Brief Pain Inventory
SF-COMPAT: Short-Form Comprehensive Pain Assessment Tool
QST: Quantitative sensory testing
EEG: electroencephalography
VAS: Visual analogue scale
SF-MPQ: Short-Form McGill Pain Questionnaire
EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
HADS: Hospital Anxiety and Depression Scale
PGIC: Patient Global Impression of Change
PROMs: Patient Reported Outcome Measures

Table 1. Types of interventions for pain in chronic pancreatitis in randomised controlled trials

Type of intervention	Number of studies	Number of RCTs
Analgesic drugs	12	9
Enzymes	9	6
Antioxidants	9	6
Nutrition	4	0
Radiotherapy	1	1
Neuroablative procedures[a]	13	7
Endoscopic[b]	35	2
Surgical[c]	76	7
Total	**159**	**38**

RCTs: randomised controlled trials.
[a] Coeliac plexus neurolysis or block, thoracic splanchnic nerve division, acupuncture, transcutaneous electric nerve stimulation, spinal cord stimulation, transcranial magnetic stimulation and intrathecal narcotic infusions.
[b] Clearing the pancreatic duct via lithotripsy or endoscopic stone removal, dilating strictures, placing of stents or a combination of endoscopic approaches.
[c] Decompression of the pancreatic duct, resection of the pancreas or a combination of both.
This table has been adjusted from (26)

Table 2. Supplemental domains for chronic pain assessment
Role functioning (work and education)
Interpersonal functioning (relationships)
Pharmacoeconomics and health care utilization
Biological markers (sensory testing, imaging, genetic markers etc.)
Coping
Clinician or surrogate ratings of global improvement
Neurophysiological assessment of cognitive/motor function
Suffering and other end-of-life issues

Table 3. Some recommended questionnaires for four of the core domains in the IMMPACT guidelines	Relevant change
Pain	
a) 11 (0-10) point numeric rating scale (including diaries)	≥ 30% decrease
b) Rescue analgesics	
c) Categorical rating of pain intensity (none, mild, moderate, severe) where numerical ratings are problematic	
Physical functioning	
a) Multidimensional Pain Inventory Interference Scale	≥ 0.6 point decrease
b) Brief Pain Inventory interference	1 point decrease
Emotional functioning	
a) Beck Depression Inventory	≥ 5 point decrease
b) Profile of Mood States	
Total Mood Disturbance	≥ 10-15 point decrease
Specific subscale	≥ 2-12 point change
Global rating	
Patient Global Impression of Change	Much improved

Table 4. Most important standards recommended to improve assay sensitivity	
Characteristics	**Considerations**
Pain	
a) Duration	≥ 10 months, no maximum
b) Baseline intensity	≥ 4 on numeric rating scale, maximal < 9
c) Variability	less variability likely improves assay sensitivity
d) Diary compliance	≥ daily diaries/week
e) Psychopathology	exclude certain disorders
f) Subject training	consider expectations and training protocols
Study design	
a) Cross-over designs	allow smaller sample sizes and may improve assay sensitivity
b) Enriched enrolment	improves sensitivity in certain instances
c) Treatment groups	generally < 3
d) Rescue medication	when necessary but limit usage
e) Baseline duration	> 1 week
f) Study duration	12 weeks for confirmatory trials, shorter for proof-of-consent
Study site	
a) Number of sites	as few as possible
b) Staff training	standardized training protocols
c) Infrastructure	high priority for international collaborations
Outcome measurements	
a) Frequency	daily ratings of average pain last 24 hours, consider weekly rating backups
b) Mode and order of administrations	research agenda

Table 5: Patient Reported Outcomes (PROs) utilized in past or current studies for assessment of pain and pain-related morbidity in children with PACP

Category	Instruments Used
Pain Severity	Faces Pain Rating Scale(143)
	Numeric Pain Rating Scale(147)
Pain Characteristics	Character of pain (intermittent or constant)(143)
	Frequency of pain(143)
	Improved/Same/Worse after intervention(146)
	Abdominal Pain Index [standardized 4 question instrument] (148)
Functional Impact of Pain	Missed school(143)
	Emergency Department/Hospital visits(143)
	Child Activity Limitations Interview-9 question (CALI-9)(148)
	PROMIS Pain Interference(147)
Health Related Quality of Life	Child Health Questionnaire Child Form (CHQ-87)(143)
	Child Health Questionnaire Parent Form (CHQ-50)(143)
	Short Form- 36(146)
	Short Form- 12(147)
	Short Form- 10 for Children (<12 years of age)(151)
Mental Health/ Emotional Impact	Child Behaviour Checklist (CBCL)(143)
	Youth-Self Report Form (YSR/11-18)(143)
	PROMIS Emotional Distress Scale (pediatric)(148)
	PROMIS Depression (paediatric)(147)
	PROMIS Anxiety (paediatric)(147)
	Child Self Efficacy Scale(148)
	Beth Adolescent Pain-Parental Impact (BAP-PIQ)(148)

Table 6. General pain assessment tools used in clinical studies of patients with PACP

General pain assessment tools	Number of studies	Number of RCTs	Reference
Unidimensional			
Pain visual analogue scale (VAS) (intensity)	58	22	(218)
Pain numerical rating scale (NRS) (intensity)	11	2	(219)
Pain intensity categories (mild, moderate, severe)	17	7	(220)
Pain improvement/relief categories[b]	14	1	(221)
Pain pattern (constant/intermittent)	12	2	(222)
Postprandial pain (yes/no or intensity)	5	3	(223)
Frequency of pain attacks[c]	11	4	(224)
Bidimensional			
(Number of days with pain) x (median pain VAS)	1	1	(225)
(Daily pain duration) x (median pain VAS)	1	1	(226)
(Number of hours of pain) x (median pain VAS)	1	1	(227)
(Degree of frequency) x (median pain VAS)	1	0	(228)
(Pain frequency) x (pain severity)	2	0	(229)
Multidimensional			
McGill Pain Questionnaire (full and short-form)	5	3	(226)
PainDetect Questionnaire (PDQ)	1	1	(15)
Pain score (intensity, frequency and consequences of pain)[d]	1	0	(230)
Impact of pain			
Quality of life scales (EORTC, EuroQol, SF-36/SF-12)[e]	27	6	(231–233)
Brief Pain Inventory (BPI)	2	1	(15)
Pain Disability Index (PDI)	2	1	(234)
Pain Coping and Cognition List (PCCL) Questionnaire	1	0	(231)

These tools were not developed specifically for the assessment of pain in chronic pancreatitis

[a] Reference in which the pain assessment tool was first used pre- and post-intervention in chronic pancreatitis.

[b] Pain improvement/relief categories: Complete/partial/none; none/transient/moderate/asymptomatic; worse/unchanged/improved; complete/major/absence; relief/considerable/improvement.

[c] Frequency assessed as: none/daily/weekly/monthly/yearly; painful days per month; pain attacks per year; occasional/frequent/daily/severe.

[d] Intensity, frequency and consequences of pain are individually graded on a 0-8 scale and the sum of the scores determine final pain score: mild pain (score of 1-8) moderate pain (score of 9-14); severe pain (score of 15-24).

[e] European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30); EuroQol questionnaire; Medical Outcomes Study Short Form- 36 Health Survey (SF-36) and Short Form-12 Health Survey (SF-12).

This table has been adjusted from (26)

Table 7. Specific assessment tools used in clinical studies of PACP

Specific pain assessment tools	Number of studies	Number of RCTs	Reference[a]
Izbicki pain score[b]	15	6	(57)
Ammann (Type A & B)[c]	5	0	(20)
Type A-E[d]	1	1	(239)
Group 1-3 pain patterns[e]	1	0	(240)
QLQ-PAN26 / EORTC QLQ-C30[f]	2	1	(192)
COMPAT[g]	1	0	(238,241)
PANQOLI[h]	2	0	(193)
AIIMS pain score[i]	3	2	(59)

[a] Reference in which the pain assessment tool was first developed specifically for patients with chronic pancreatitis.
[b] Pain score comprising of pain visual analogue scale (VAS), frequency of pain attacks, analgesic medication and duration of disease-related inability to work.
[c] Type A pain pattern (Intermittent) typically observed in acute relapsing pancreatitis, is short-lived pain episodes usually lasting <10 days and separated by long pain-free intervals of several months to >1 year. Type B pain (Constant) is characterized by prolonged periods of persistent (daily) pain and/or clusters of recurrent severe pain exacerbations. Typically severe pain occurred for 2 or more days per week for at least 2 months. May follow A type pain episode.
[d] Type A: Episodes of mild to moderate pain, usually controlled by medication; Type B: Constant mild to moderate pain usually controlled by medication; Type C: Usually pain free with episodes of severe pain; Type D: Constant mild pain plus episodes of severe pain; Type E: Constant severe pain that does not change.
[e] Group 1: constant pain; Group 2: Constant pain with acute exacerbations; Group 3: Only acute exacerbations and no constant pain.
[f] Quality of Life Questionnaire-Pancreas Modification (QLQ-PAN26) to be used together with European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).
[g] The comprehensive pain assessment tool (COMPAT) addresses all key aspects of pain and includes the short-form.
[h] Pancreas Quality of Life Instrument (PANQOLI) is the first disease-specific instrument to be developed and validated for the evaluation of quality of life in chronic pancreatitis patients.
[i] The All India Institute of Medical Sciences (AIIMS) pain score included frequency of pain and treatment/severity (no treatment/oral analgesics/parenteral analgesics/hospitalisation into a combined 0-12 score
This table has been adjusted from (26).

Table 8. Aspects of pain in general multidimensional tools and chronic pancreatitis specific tools used to assess pain in chronic pancreatitis

Aspects of pain	**General multidimensional tools**		**CP-specific tools**					**Impact of pain tools**			
	MPQ[a]	PDQ[b]	Izbicki[c]	Amman	Type A-E	Group 1-3	COMPAT	BPI[d]	PDI	PCCL	HRQOL scales
Key reference	(219)	(15)	(57)	(20)	(239)	(240)	(92,238)	(15)	(234)	(240)	(192,231–233)
Duration of pain							■				
Location of pain		■					■	■			
Radiation of pain		■					■				
Triggers/exacerbators of pain	F	■					■				
Pain pattern (Continuous/Intermittent)	F	■		■	■	■	■				
Objective measure of pain intensity[e]	S	■	■				■	■			
Subjective estimate of intensity of pain[f]	F				■	■	■				■
Frequency of pain attacks			■	■			■				
Description of pain	B	■					■				
Associated symptoms with pain	B	■					■				
Postprandial pain							■				
Analgesic use			■				■	■			
Relieving factors of pain	F						■	■			
Ability to work/occupation status			■				■	■	■		■
Effect on daily activities/function							■	■	■	■	■
Effect on mental health							■	■		■	■

Shaded boxes indicate aspects of pain that were included in the corresponding pain assessment tool used in pain evaluation in chronic pancreatitis.

PDI: Pain disability index; PCCL: Pain coping and cognition list; HRQOL: Health related quality of life scales (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and Quality of Life Questionnaire-Pancreas Modification (QLQ-PAN26); EuroQol questionaire; Medical Outcomes Study Short Form-36 Health Survey (SF-36) and Short Form-12 Health Survey (SF-12).

a McGill pain questionnaire (MPQ) refers to full McGill (F), short-form McGill (S) and both (B).

b PainDetect Questionnaire (PDQ) uses pain Numerial Rating Scale (NRS) for assessment of pain intensity.

c Izbicki uses pain Visual Analogue Scale (VAS) for assessment of pain intensity.

d Brief Pain Inventory (BPI) uses pain NRS for assessment of pain intensity.

e Pain VAS, NRS or descriptor.

f Mild, moderate or severe

This table has been adjusted from (26)

Table 9. Criteria for the evaluation of pain in chronic pancreatitis

		International consensus guidelines recommendations for pain evaluation			
		Italian	German, Swiss and Austrian	Belgian	PancreasFest
Evaluation of pain proposed by AGA	Duration of pain dating back to the first episode				
	Character of pain: intermittent vs. daily; frequency if intermittent				
	Subjective estimation of intensity of pain: mild, moderate, or severe				
	Objective measurement of pain: visual analogue or descriptor (e.g.,1-5; 1-10)				
	Use of narcotics and other medications to treat pain				
	Evaluation of addiction to narcotics				
	Documentation that other diseases have been excluded that could				
	Measurement of quality of life including work performance, social interaction, and family interaction				
Eight additional aspects of pain from the literature	Location of pain				
	Radiation of pain				
	Triggers/exacerbators of pain				
	Description of pain				
	Associated symptoms of pain				
	Postprandial pain				
	Relieving factors of pain				
	Effect on mental health				

Shaded boxes indicate aspects of pain that were included in the corresponding international consensus guidelines for pain evaluation in chronic pancreatitis.
This table has been adjusted from the original table in (26).

Table 10. Pain assessment tools for pain evaluation in chronic pancreatitis

Guidelines	Pain assessments tools recommended							
	Pain VAS	Amman	Izbicki pain score	MPQ	PROMIS	SF-12	EORTC QLQ-C30	PANQOLI
Italian		EL 2b; RG B				EL 1b; RG B	EL 1b; RG B	
German, Swiss and Austrian	EL 1b; RG B		EL 1b; RG B				EL 1b; RG B	
Belgian								
Pancreasfest	EL 2b; RG C			EL 2b; RG C	EL 2b; RG C	EL 2b; RG C		EL 2b; RG C

These pain assessment tools for pain evaluation in chronic pancreatitis are recommended by international consensus guidelines (243–246)
VAS : Visual analogue score.
MPQ: McGill Pain Questionnaire.
PROMIS: NIH Patient-Reported Outcome Measurement Information System
SF-12: Medical Outcomes Study Short Form _12 Health Survey
EORTC: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
PANQOLI: Pancreas Quality of Life Instrument
Based on Oxford Centre for Evidence-Based Medicine: EL . Evidence level; RG . Grades of Recommendation.
Shaded boxes indicate the pain assessment tools that were recommended by each individual international consensus guidelines for pain evaluation in chronic pancreatitis.
This table has been adjusted from (26).

Table 11. Research questions for further research into pain assessment and pain treatment in patients with PACP

Identified research gaps: categories	Suggestion for future research
Questionnaire	➢ What is the best pain assessment instrument in PACP? ➢ Which are the most valid patient and disease related domains to be considered in future clinical trials? ➢ Which is most sensitive and yet practical QST method for bedside use? ➢ How do cultural and language issues interfere with pain assessment? ➢ How can the balance between effects and side effects be integrated in assessment of efficacy of pain treatment?
Interventions	➢ Can the outcome of pharmacotherapy, invasive treatments and neuromodulation be predicted in order to tailor treatment of PCAP to the individual patient? ➢ What is the role of placebo and sham interventions in randomized controlled trials? ➢ How can pain assessment be used to evaluate how many endoscopic interventions and during which time period should be allowed before surgery is indicated? ➢ What is the impact of the pre-interventional expectation on the outcome after interventional treatment on the pain relief?
Psychological comorbidities	➢ What is the optimal assessment of anxiety and depression, since this has a great impact on the treatment and consequence of the disease? ➢ Which other domains (e.g., pain catastrophizing, coping mechanisms, social support, sleep etc.) have impact on treatment outcome?
Paediatrics	➢ What is the impact of family dynamics (by collection of both parent and child histories) on pain assessment outcome in children with PACP? ➢ What is the role of neurodevelopment on pain assessment in children with PACP? ➢ What is the role of QST in the evaluation of children with PACP?

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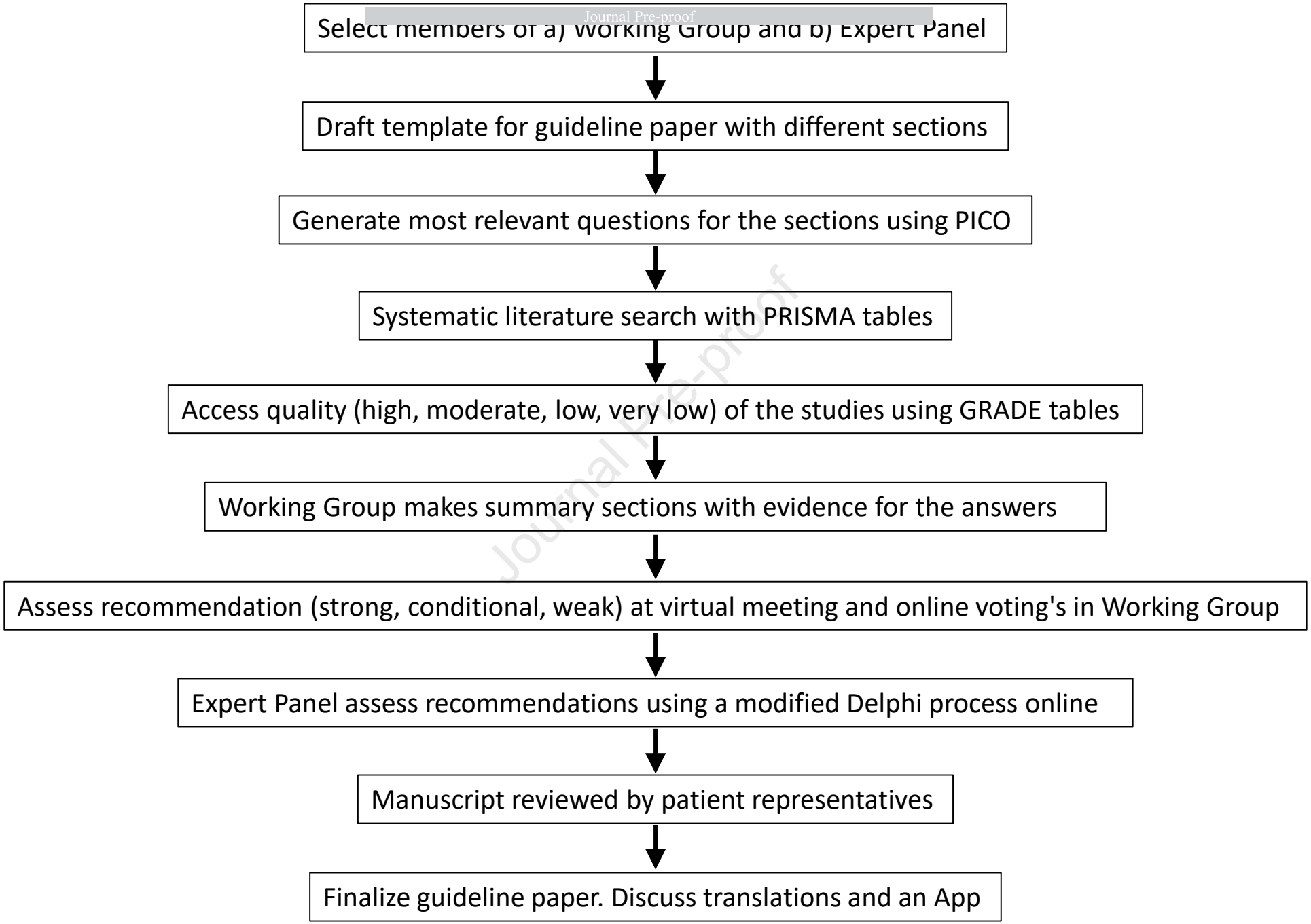

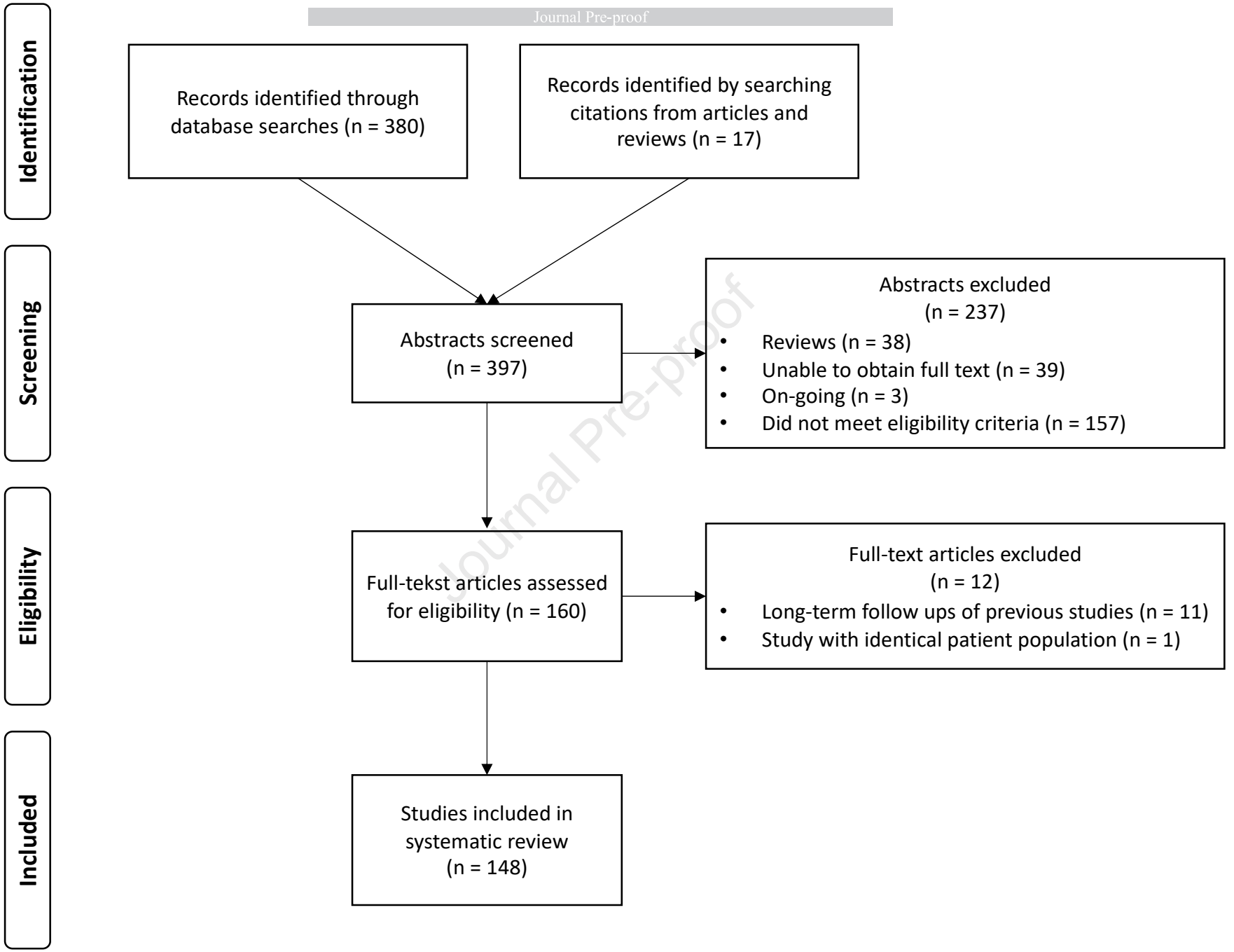

Strongly disagree	Disagree	Moderately disagree	Mildly disagree	Undecided	Mildly agree	Moderately agree	Agree	Strongly agree
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**