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Patient Related Outcomes for Interstitial Cystitis/Bladder Pain Syndrome Recommendations for Clinical Trials and General Urology Practice

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ABSTRACT

Introduction: The goal of this committee of the Interstitial Cystitis/Bladder Pain (IC/BPS) Consensus Group was to address the use of patient related outcomes (PROs) in IC/BPS.

Methods: Priority areas of concern and related PICO (Population, Intervention, Comparison, Outcome) questions were addressed based on literature review, committee discussion and consensus group feedback. Consensus recommendations were developed regarding PROs and PRO Measures (PROMs) for the critical PICO questions.

Results: PICO questions addressed 4 critical areas of concern: PROs, clinical trial primary endpoints, secondary endpoint PROMs and questionnaires for general practice management. The committee made 12 recommendations regarding outcomes in IC/BPS research and clinical practice.

Discussion: The most important recommendation was the unmet need to develop and validate a better IC/BPS specific PRO, based on unbiased patient qualitative research methodology. At the present time, the Numerical Rating/VAS pain scales, voiding diaries and global response assessment are recommended for primary endpoint outcomes in clinical trials. The suggested composite IC/BPS specific PROM is the Genito Urinary Pain Index (GUPI) while the Interstitial Cystitis Symptom Index/Problem Index can be used for trial comparisons. If appropriate, generic PROMs that describe and measure pain, quality of life, sexual, and psychosocial parameters are suggested. Until a validated PRO is developed, the NIH GUPI or the Pain Urinary Frequency (PUF) questionnaire provides reasonable clinical evaluation of patients in standard urology practice.

Conclusion: PROMs are currently available for use in clinical trials and general practice, but more research is required to create better IC/BPS PRO-based outcome measures.

1 | Introduction

High quality care for our interstitial cystitis/bladder pain syndrome (IC/BPS) population requires patients to provide information regarding their symptoms, general feelings and response to treatment. The "holy grail" of patient health reporting is the concept of patient reported outcomes (PROs). In the IC/BPS field, identifiable, validated and reliable PRO measures (PROMs) have become important in providing this information [1, 2].

IC/BPS is an enigmatic urology condition that encompasses both perceived bladder pain and urinary symptoms [3]. Except for possibly those identified with Hunner lesions, the majority of patients suffer from an ill-defined syndrome rather than a proven disease. There are no truly objective findings or markers of disease, and the diagnosis is made based on symptoms, physical examination and exclusion of confusable diseases [3]. The symptoms are highly variable between patients. Typically, patients diagnosed with IC/BPS have increasing pain with bladder filling and urinary storage symptoms (urgency and frequency). However, patients may present with other bladder pain (e.g. constant bladder pain or bladder/urethral pain with urinating) and urinary (e.g. dysfunctional voiding including urinary retention) symptom patterns. To complicate the clinical picture even more, most patients have associated local and generalized pain related medical conditions such as pelvic floor dysfunctional pain, Irritable Bowel Syndrome, Chronic Fatigue Syndrome etc [4] and many patients experience sexual dysfunction primarily related to sexual pain [5]. Furthermore, we now realize that psychosocial factors such as depression, anxiety, stress and maladaptive coping modulate and/or propagate the syndrome [6]. Although all patients may present with bladder pain and urinary symptoms, every patient's clinical picture is unique with differing clinical phenotypes [7, 8]. It is no wonder that there has been so much difficulty in developing and validating generally acceptable outcome instruments to be used in IC/BPS clinical trials and general clinical practice.

2 | Methods

The goal of our committee was to address the use of outcome measures used in the management of patients with IC/BPS in clinical research and general urology practice. The committee was composed of five urologists with basic science and clinical expertise in IC/BPS (RE, SH, DJ, SP, JCN), one IC/BPS patient (CK) and two urology students (MN, BH). The outcomes committee compiled a list of priority areas of concern to be addressed in a comprehensive manner based on a literature review and consensus discussion.

Corresponding clinical questions were formulated within those areas using a modified PICO (population, intervention, comparison, outcome) format. These areas include Patient Related Outcomes (PROs), disease-specific Patient Related Outcome Measures (IC/BPS specific PROMs) and generic PROMs.

The focused literature review identified key development and validation studies of specific and general IC/BPS outcomes and how these outcomes were employed in clinical studies (particularly randomized controlled trials). The committee provided their personal expert opinions and individual research experience over e-mail discussion followed by two ZOOM meetings

Following incorporation of feedback during the International IC/BPS consensus meeting, the committee made specific and general recommendations regarding PROMs associated with each of the critical PICO questions. The recommendations (including strength of recommendation) were based on the certainty of the evidence, the validation of the instrument, the reliability of the outcome in research and practice and the expertise and experience employing these outcome instruments in both clinical research and clinical practice scenarios.

It is important to recognize that the panel did not set out to create a guideline, but rather consensus-based research and practice recommendations regarding choosing PROs and PROMs in IC/BPS clinical trials and general urology practice. These recommendations will evolve as more outcome research in IC/BPS is available.

3 | Results

The literature search identified multiple PROs, PROMs, questionnaires and outcomes that have been used in research studies and clinical practice. A summary of the most used outcome measures including description, validation and pertinent references is shown in Table 1.

The committee identified 4 critical areas of interest to the goals related to outcomes in IC/BPS. These included (1) PROs for both clinical trials and clinical practice; (2) Primary outcome endpoints for clinical trials; (3) Secondary (and tertiary) PROMs for research; and (4) Best IC/BPS symptom questionnaires for characterizing and following patients in general urology practice.

Corresponding clinical questions were formulated within those areas using a modified PICO format [39]. The detailed modified PICO questions are listed in Table 2.

Based on the literature review, committee expertise and experience and feedback from the IC/BPS Consensus meeting, 12 recommendations (including the strength of recommendation) were decided upon (Table 3). These are not to be construed as guideline recommendations but rather practical recommendations to consider when designing clinical studies and/or trials or following patients in general urology practice.

4 | Discussion

It is risky and likely an impossible proposition to recommend a single outcome instrument that can be employed successfully to describe and follow patients suffering from IC/BPS. The outcomes committee recommendations regarding outcome measures that should be considered in IC/BPS are outlined in Table 3. They were based on what the committee members believed were the most critical areas to be examined and then formulated by addressing PICO type questions.

TABLE 1 | Background summary of IC/BPS patient related outcome measures.

Outcome	Description	Validation summary	Pertinent reference(s)
Standard Accepted Nonspecific Outcomes			
Numerical Rating Scale (NRS) or Visual Analogue Scale (VAS) Pain	11-point (NRS) or point on a line (VAS) ranging from 0 (no pain) to 10 (pain as bad as you can imagine).	Accepted validated values for severity of pain.	Jensen MP et al. (1999) [9] Scott J and Huskisson EC. (1976) [10]
Voiding Diary	Daily recording of void events, volumes, and associated urgency (and/or pain) over 24 h. May also include fluid intake recording.	BPS/IC patient diaries results differ from OAB patients in regard to maximal voiding capacity and frequency.	Kim SH et al. (2014) [11]
Global Response Assessment (GRA)	7 grade Global Response Assessment (GRA) evaluates patient's clinical condition relative to baseline. Patients self-report their perception of overall difference in IC/BPS pain and urinary symptoms without delineating actual symptoms.	Validated with O'Leary ICSI and Likert scale. Unique global response instrument in having equal number of positive and negative choices (symmetrical).	Propert KJ et al. (2002) [12]
IC/BPS Composite Scoring Indices			
O'Leary-Sant Interstitial Cystitis Symptom and Problem Index (ICSI and ICPI)	The ICSI measures frequency of IC/BPS symptoms, while the ICPI assesses the magnitude of problems resulting from these symptoms. Both are four-item scales. Total scores range from 0–20 and 0–16, respectively,	Internal consistency, construct validity and test-retest reliability evaluated and show both reliable and reproducible measures of outcomes.	O'Leary MP et al. (1997) [13] Lubeck DP et al. (2001) [14]
Wisconsin IC Questionnaire	Includes 7 symptoms of IC during the day rated on a 0-6 scale; total score of 0–42. This is coupled with an 18 reference symptom item scale of symptoms not associated with IC to make a 25-item checklist.	In small validation studies, the scale was found to have good face validity, internal consistency but recommendations for adding further symptoms (e.g. pelvic item) to the current 7-time IC construct.	Goin JE et al. (1998) [15]
NIH MAP Genitourinary Pain Index (GUPI)	Questionnaire characterizing GU pain in men and women (10 item pain scale 0–23), urinary symptoms (2 item score 0–10) and quality of life items (3 item subscale score 0–12); total score range of 0–45.	A robust validation study (compared against the ICSI/PI) indicated the GUPI to have good discriminate validity, concurrent validity to distinguish between chronic prostatitis, IC and those with incontinence. A valid and reliable instrument to characterize the degree of symptoms in both men and women with GU complaints. In a small post hoc sub study showed responsiveness to change.	Clemens JQ et al. (2009) [16]
Bladder Pain Interstitial Cystitis Symptom Index (BPIC-SS)	8 item score assessing urgency, urinary frequency, and bladder pain and pressure. Items distinguished between bother associated with daytime and nighttime frequency, as well as urgency specifically driven by pain. Score range is from 0–38.	BPS, Overactive Bladder, and Healthy Control patients were concurrently assessed via BPIC-SS and ICSI and BPIC-SS and PUF. BPIC-SS appeared more discriminative than PUF or ICSI. BPIC-SS also demonstrated good test-retest reliability and clinical validity. It has not yet been shown to measure reliable responsiveness to change.	Humphrey L et al. (2012) [17]

(Continues)

TABLE 1 | (Continued)

Outcome	Description	Validation summary	Pertinent reference(s)
Apollo Clinical Scoring System	A six-item weighted clinical score looking at urgency, frequency, nocturia, pain, sexual dysfunction and psychological impact. Pain ranging from 0–20, nocturia 0–10 while the remaining clinical factors have a range from 0-5: total score 0–50.	When compared to ICSI, this scale had better test-retest reliability, internal consistency and some responsiveness to change. Primarily developed and validated from a single center.	Taneja R et al. (2024) [18]
RAND Interstitial Cystitis Epidemiology Study Questionnaires (RICE)	Questionnaire with 2 definitions for BPS/IC; one for high sensitivity and a second for high specificity for BPS/IC.	This is not an outcome measure but rather a diagnostic questionnaire.	Berry SH et al. (2011) [19]
Pain Urgency Frequency Questionnaire (PUF)	Evaluates pelvic pain, urinary urgency, frequency, and any pelvic pain associated with sexual intercourse. Evaluates both severity and bother level of each symptom on a 0–4 scale.	High PUF scores were found to correlate directly with higher likelihood of a positive potassium sensitivity test.	Parsons CL et al. (2002) [20]
Other e.g. Urgency, Pelvic Floor Dysfunction, Pelvic Pain, Lower Urinary Tract Symptoms			
Patient Perception of Intensity of Urgency Scale (PPIUS)	A 5-point scale designed for measurement of both urinary urgency and urge incontinence.	Validity only tested in Overactive bladder patients.	Notte SM et al. (2012) [21]
Pelvic Floor Distress Inventory (PFDI-20)	Evaluates the severity and bother associated with various pelvic floor conditions, including urinary incontinence, pelvic organ prolapse, and fecal incontinence.	Validated in multiple studies and is widely used in clinical practice to gauge the distress caused by pelvic floor disorders, including pelvic pain and to monitor treatment outcomes.	Gilleran JP et al. (2011) [22]
Electronic Personal Assessment Questionnaire-Pelvic Floor (ePAQ-PF)	Has been used to measure bladder pain in women with PFDs.	Validated in women with pelvic floor disorders and found to have high internal reliability.	Jones GL et al. (2008) [23]
Lower Urinary Tract Dysfunction Research Network Symptom Index-10/29 (LURN SI-10/29)	Questions measure full spectrum of LUTs in research (SI-29) and clinical practice (SI-10). They include questions focused on bladder pain (for abbreviated SI-10 a single question regarding pain on bladder filling.	Validated with GUPI, PFDI-20 and AUA. Symptom Index and demonstrated expected differences between men and women experiencing LUTS.	Cella D et al. (2019) [24] Cella D et al. (2020) [25]
General Pain Composite Instruments			
Brief Pain Inventory (BPI)	Assessment originally developed for cancer related pain that measures pain intensity and how pain interferes with functioning. 0–10 numerical scale	Validated in a cohort of patients with chronic pain with acceptable internal consistency. It was not consistent enough to be used alone to make treatment decisions but could be used for assessing treatment outcome	Tan G et al. (2004) [26]

(Continues)

TABLE 1 | (Continued)

Outcome	Description	Validation summary	Pertinent reference(s)
McGill Pain Questionnaire (MPQ)	Assesses sensory and affective pain dimensions and overall pain severity. The questionnaire consists of 15 single-word descriptors, with 11 related to the sensory dimension of pain and 4 related to the affective dimension. Total scores range from 0–45.	Validated in several patient populations including back pain, chronic pain, cancer, arthritis, and musculoskeletal conditions. Modest ability to discriminate between improved and not improved patients (musculoskeletal conditions).	Strand LI et al. (2008) [27]
Quality of Life (QoL)			
SF-36 Health Survey (SF-36)	36 item questionnaire that covers eight health domains related to quality of life.	Validated in the original Medical Outcomes Study and later in several patient populations. SF-36 has high reliability.	McHorney CA et al. (1993) [28]
SF-12 Health Survey (SF-12)	Created to reduce burden of response of SF-36. 12 questions cover the same domains of health as SF-36.	Validated against the SF-36.	Ware J Jr et al. (1996) [29]
EuroQol-5 Dimension (EQ-5D)	Preference based health related QoL measure to assess five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Includes both a descriptive questionnaire and VAS.	Validated in several patient populations and languages.	Rabin R and de Charro F. (2001) [30]
		Validated for OAB and Chronic Pelvic Pain.	Shaddoud A. (2022) [31]
Psychosocial Parameter Instruments			
Depression/Anxiety questionnaires (HADS)	14 item questionnaire designed to be more sensitive to mild forms of psychiatric disorders. Each item is scaled on 4 points, ranging from 0 to 3. Separate subscale each for anxiety and depression.	Each subscale correlates well with self-assessment questionnaires or external criteria for either anxiety or depression. No single accepted cutoff score. Treatment validation in multiple patient groups, particularly in patients with high initial scores.	Herrmann C (1997) [32]
The Centre for Epidemiologic Studies Depression Scale (CES-D)	A brief self-report measure of current depressive symptomology. It is a 20-items cale in which the individual rates the frequency of each symptom over the past week.	An optimal cutoff score of 27, recommended to discriminate between depressed and nondepressed chronic pain patients.	Geisser ME et al. (1997) [33]
The Patient Health Questionnaire-9 (PHQ-9)	A nine-item self-report measure assesses the frequency of experiencing nine main depressive symptoms based on the DSM-IV. Ratings ranged from 0 (not at all) to 3 (nearly every day); total scores from 0–27.	Validated by interview with blinded mental health professional. Construct validity was assessed by using Short Form General Health Survey (SF-20). PHQ-9 also was determined to have utility for diagnosing mental disorders.	Spitzer RL et al. (1999) [34]
Catastrophizing Score (PCS)	A 13-item questionnaire in which participants rate the frequency of experiencing specific feelings or thoughts during past painful experiences on a five-point scale. The PCS consists of three subscales (rumination, magnification, and helplessness) and a total score from 0–52.	Validated and demonstrates high test-retest reliability for assessing catastrophizing ideation.	Sullivan MJL et al. (1995) [35]

(Continues)

TABLE 1 | (Continued)

Outcome	Description	Validation summary	Pertinent reference(s)
State-Trait Anxiety Inventory	20 item assessment with measures of state and trait anxiety. 1–4 point scale for each item.	Validated to be an adequate measure for anxiety in research and clinical settings. Used to phenotype BPS/IC patients and controls in several clinical studies.	Speilberger CD et al. (1983) [36]
Perceived Stress Scale (PSS)	14 item assessment of the degree to which situations in a person's life are perceived as stressful. 7 items are positively stated and have their scores reversed to determine total score.	A better predictor of psychological symptoms than life-event scales. Has been utilized in IC/BPS patients.	Rothrock NE et al. (2001) [37]
Female Sexual Function Index (FSFI)	19 item questionnaire with 6 separate domains to assess desire, arousal, lubrication, orgasm, satisfaction, and pain as it relates to sexual female sexual arousal and function.	High test-retest reliability and discriminant validity in study comparing female sexual arousal disorder patients to normal controls. It also showed divergent validity in the original study.	Rosen R et al. (2000) [38]

TABLE 2 | Modified PICO* questions addressed by the Outcomes subcommittee.

Question #1: In patients with IC/BPS in clinical trials, do contemporary Patient Related Outcomes compared to presently validated pain and urinary questionnaires provide more accurate primary and/or secondary outcomes?

Question #2: In patients with IC/BPS in clinical trials, how do validated pain scales and voiding diaries compare to presently available composite questionnaires for primary outcomes?

Question #3: In patients with IC/BPS in clinical trials, which (composite) domain instruments (compared to each other) are best for use as secondary outcomes?

Question #4: In patients with IC/BPS followed in standard clinical practice, which of the various composite domain questionnaires are best in terms of practical utility outcomes in clinical follow-up?

*__PICO__: **P**opulation – IC/BPS patients; **I**ntervention – Patient Related Outcome Measures (PROMs); **C**omparison – to other PROMs; **O**utcome – Consensus-based validation and reliability utility in research and clinical practice

4.1 | Patient Related Outcomes (PROs)

It is recognized that PROs are the "holy grail" of outcome evaluation in clinical trials and clinical practice. While the committee were impressed with several of the IC/BPS PROMs presently available, we could not identify any correctly designed and validated PROs specific to IC/BPS. The Bladder Pain Interstitial Cystitis Symptom Index (BPIC-SS) was developed using a methodology incorporating both qualitative and quantitative approach [17], while the Genitourinary Pain Index (GUPI) modified from the Chronic Prostatitis Symptom Index (CPSI) and has been shown to be responsive to change in an unreplicated post hoc analysis of a small treatment study [16]. It should be our top priority to develop evidence-based PROs in IC/BPS (or modify and/or validate existing PROMs). The PRO would follow a patient centered approach to comprehensively assess the impact of treatment [40, 41]. Once such a PRO has been validated and found to be reliable for clinical follow-up it could be used for either a primary (or to complement a primary) or secondary outcome in a clinical trial. Such a PRO would prove invaluable for follow-up in clinical practice. The development and validation of IC/BPS PROs is beyond the scope of our objective. We recommend that a mixed method study design based on both quantitative like interview, focused group discussion and qualitative approaches should be our next essential step in this field [42].

4.2 | Primary Endpoint Outcomes for Clinical Studies/Trials

The Numerical Rating Scale (NRS) or Visual Analogue Scale (VAS) of pain is the most accepted and used measure to describe pain at baseline and during follow up in clinical pain trials [9, 10, 43]. This 11-point measure should be strongly considered as a primary outcome in clinical trials of IC/BPS treatments. The severity of pain can be described as a point in time, average or maximum pain over a predetermined time

TABLE 3 | Consensus recommendations for Outcome Measures for IC/BPS studies, trials and general clinical practice. A STRONG recommendation implies that the outcomes committee believed that the vast majority of experts would make this recommendation based on available evidence and clinical experience. A CONDITIONAL recommendation was made when the outcome committee believed most experts would opt for the recommendation based on the evidence, however, a substantial minority of experts would choose an alternative plan.

Recommendation #1: The IC/BPS research community should commit to developing a true PRO, employing unbiased patient orientated qualitative research (STRONG).
Recommendation #2: Numerical Rating Scale or Visual Analogue scale of pain described as 0-10 should be strongly considered as a primary outcome endpoint in clinical trials of IC/BPS treatments (STRONG).
Recommendation #3: Voiding diaries (frequency volume charting) for a minimum of 3 days at each time point should be strongly considered as a primary outcome endpoint in clinical trials of IC/BPS treatments (STRONG).
Recommendation #4: Composite primary endpoints should be considered (CONDITIONAL).
Recommendation #5: A 7-point Global Response Assessment (GRA) should be considered as either a co-primary endpoint or one of the most important major secondary endpoints (STRONG).
Recommendation #6: The O'Leary Sant Interstitial Cystitis Symptom Index/Problem Index (ICSI/PI) can be considered as an anchor questionnaire so that patients enrolled in a clinical trial can be compared to other populations in historical clinical trials (CONDITIONAL).
Recommendation #7: The National Institutes of Health Genito Urinary Pain Index (NIH-GUPI) should be considered as secondary endpoint outcome (STRONG).
Recommendation #8: Clinical trials evaluating treatment outcomes in IC/BPS should incorporate a Quality-of-Life assessment tool (STRONG).
Recommendation #8a. The two most employed quality of life assessment instruments recommended for IC/BPS clinical trials are the SF-12 or SF-26 Health Survey (SF-12; SF-36) or EuroQol-5 Dimension (EQ-5D) questionnaire (STRONG).
Recommendation #9: Clinical trials evaluating treatment outcomes in IC/BPS should consider a validated composite pain assessment outcome (STRONG).
Recommendation #9a. The two most employed pain assessment instruments recommended for IC/BPS clinical trials are the McGill Pain Questionnaire (MPQ) or the Brief Pain Inventory (BPI) (STRONG).
Recommendation #10: Sexual Function associated with IC/BPS should be considered for evaluation as tertiary outcomes (CONDITIONAL).
Recommendation #11: Psycho-social parameters associated with IC/BPS should be considered for evaluation as tertiary outcomes (CONDITIONAL).
Recommendation #12: A validated clinical questionnaire for patient baseline and follow-up assessment is recommended as an important component of good patient practice in managing patients with IC/BPS in general practice (STRONG).
Recommendation #12a: The National Institutes of Health Genito Urinary Pain Index (NIH-GUPI) or the Pain Urgency Frequency Questionnaire (PUF) should be considered a useful instrument for baseline assessment and clinical follow up in patients with IC/BPS in standard clinical practice (CONDITIONAL).

period (suggested mean maximum or worse pain over a minimum of 3 days for each trial assessment interval). This single patient's rating of pain can be considered a PRO, but its major limitation is that it is not specific to IC/BPS. A patient with IC/BPS has multi-dimensional pain experience as part of the clinical experience [44, 45].

Voiding diaries (frequency volume charting) should be strongly considered as a primary outcome in clinical trials of IC/BPS [11]. The consensus is to evaluate 3 separate days for an individual outcome measurement assessment. Items of relevance for IC/BPS are (per 24 h); urinary frequency, urgency and voided volumes. It is important to know that urgency experienced by IC/BPS has another dimension compared to OAB patients – typically a gradually increasing pain or discomfort during bladder filling, leading to more frequent voiding to prevent such pain. Also of note is the variations between IC/BPS patients in storage and voiding behavior can depend on availability of toilets, activities (pre-emptive voiding before recreation, work, social activities) and fluid intake as well as individual pain avoidance voiding patterns.

The FDA-BRUDAC committee [43] has suggested that co-primary outcomes should be considered in clinical trials. However, an analysis from the Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network [46] points out that pain and urinary symptoms should be assessed separately rather than combined in a single score. The same might prove true using pain and urinary scores as a co-primary outcome.

A 7-point Global Response Assessment (GRA) has been employed as a primary endpoint, co-primary endpoint and as a secondary endpoint in published clinical trials. Patients self-report their perception of their clinical condition relative to baseline. The GRA assesses the patient's overall perception of difference in bladder pain and urinary symptoms (equal number of positive and negative choices) without identifying specific

symptoms. Responders for the GRA were typically defined as subjects reporting that they were "markedly improved" or "moderately improved" compared with baseline [12, 47].

4.3 | Composite Domain Patient Related Outcomes for Clinical Trials

The O'Leary Sant Interstitial Cystitis Symptom Index/Problem Index (ICSI/PI) [13, 14] is undoubtedly the instrument most employed in clinical trials over the course of decades of IC/BPS research, however the committee believes it has serious limitations. Scoring can be problematic, weighting of symptom domains has not been truly validated, and it is missing important domains of the IC/BPS experience. However, since it has been so widely used in clinical trials, it can be considered as an anchor questionnaire allowing patients enrolled in a clinical trial to be compared to other populations in historical clinical trials.

At present, the committee believes that the Genitourinary Pain Index (GUPI) [16] should be considered as a secondary endpoint in clinical trials. In separate questionnaires for men and women, the instrument, modified from the male based Chronic Prostatitis SI characterizes GU pain (location, frequency and severity - scale 0-23), urinary symptoms (storage and voiding items - score 0-10) and 3 impact/quality of life items (subscale score 0-12). Total score range of 0–45 for the total score indicating increasing disease severity. The GUPI has been well validated to distinguish IC/BPS from other similar urology conditions and has been found to be a valid PROM to characterize the degree of IC/BPS symptoms in both men and women. Its major limitation has been a lack of qualitative validation and sparse evaluation of its reliability in quantifying symptom change over time in multiple clinical trials.

The Wisconsin IC Questionnaire [15] was one of the first of these IC/BPS specific symptom instruments developed. This 25-item questionnaire (assesses 7 IC symptoms) has been validated (perhaps not to the rigor of contemporary validation studies), but its complexity and missing of key domains has made it less desirable for either research or clinical practice purposes.

The Apollo Clinical Scoring System [18] is a six-item clinical score which examines urgency, frequency, nocturia, pain, sexual dysfunction and psychological impact. It is simple to employ but has been designed and validated by a single group and has not achieved general acceptance at this time. This questionnaire may prove valuable with validation for discrimination and outcomes by other research groups in large clinical trial settings.

The BPIC-SS [17] is an industry generated questionnaire that appears to be more discriminative than PUF or ICSI. BPIC-SS also demonstrated good test-retest reliability and clinical validity. It has not been validated as a clinical outcome tool and has not been widely employed in clinical studies or trials.

The RAND Interstitial Cystitis Epidemiology Study Questionnaires (RICE) [19] is not an outcome measure but rather a diagnostic questionnaire that has proven useful in epidemiology studies.

Pain Urgency Frequency Questionnaire (PUF) [20] was developed by a single investigator to evaluate pelvic pain, urinary urgency, frequency, and any pelvic pain associated with sexual intercourse. The questionnaire evaluates both severity and bother level of each symptom on a 0-4 scale. It was originally evaluated against the intravesical potassium sensitivity test (PST) where a PUF score of 15 or greater was associated with 84% chance of positive PST (PST is now considered a historical IC diagnostic test). It is a useful tool in clinical practice to evaluate patients and then follow progress but not recommended for clinical trials.

The Patient Perception of Intensity of Urgency Scale (PPIUS) [21] is a 5-point scale designed for measurement of both urinary urgency and urge incontinence. While it has been used in IC/BPS clinical trials, it has not been validated in this syndrome.

Assessment of pelvic floor dysfunction, general pelvic pain and lower urinary tract symptoms (LUTs) can capture a more comprehensive picture of pelvic pain and its associated distress in women [48]. The Pelvic Floor Distress Inventory (PFDI-20) [22], the electronic Personal Assessment Questionnaire-Pelvic Floor (ePAQ-PF) [23] and the LUT Dysfunction Research Network Symptom Index-10 and 29 (LURN SI-10, 29) [24, 25] are examples of instruments that may offer valuable insights into the bladder pain component in patients with pelvic floor dysfunction and/or LUTS. The committee does not recommend these instruments for outcomes in IC/BPS clinical trials unless the intervention specifically is targeted for pelvic floor or LUTs related pain conditions.

The individual variability among patients with IC/BPS makes total scores from such composite scoring instruments problematic when assessing clinical response. As part of the MAPP Research Network, pain and bladder symptoms were assessed using the GUPI and ICSI/PI. The results suggested that pain and urinary symptoms should be assessed separately rather than combined into 1 total score [46]. This underscores the problem with composite scoring indices that combine the separate factors of pain, urinary symptoms and quality of life into a single composite score. This limitation is the major reason why such composite scores should not be used as primary outcomes.

4.4 | Other Generic PROMs Available to Investigators as Secondary or Tertiary Outcomes

The committee members strongly recommend that clinical trials evaluating treatment outcomes in IC/BPS should incorporate a Quality-of-Life assessment tool. The two most employed quality of life assessment instruments recommended for IC/BPS clinical trials are the SF-12 or SF-36 Health Survey (SF-12; SF-36) or EuroQol-5 Dimension (EQ-5D) questionnaire [28–31]. The committee also recommends that clinical trials evaluating treatment outcomes in IC/BPS should consider a validated composite pain assessment tool. The two most employed pain assessment instruments used in IC/BPS clinical trials are the McGill Pain Questionnaire (MPQ) [27] and the Brief Pain Inventory (BPI) [26].

The committee also recommends that sexual and psycho-social parameters associated with IC/BPS should be considered for

evaluation as tertiary outcomes. Recommendations of which psychosocial domains or which questionnaires should be used are beyond the scope of this committee's mandate. Examples of such measures used in IC/BPS (sexual, depression, anxiety, stress, catastrophizing etc.) [32–38] are described in Table 1.

The committee members are cognizant of the fact that patients in clinical studies and trials may be subjected to too many PROMs and that could lead to questionnaire fatigue. It is imperative that the outcomes necessary for endpoint analyses be chosen carefully for any specific intervention. This choice of instruments to be used should be based on the study/trial objectives, the intervention mechanism and the anticipated symptom changes associated with a specific study question or treatment [49].

4.5 | Symptom Questionnaires in General Urology Practice

A validated clinical questionnaire for patient baseline and follow-up assessment is recommended as an important component of good patient practice in managing patients with IC/BPS. The committee recommends either the NIH-GUPI [16] or the PUF questionnaire [20] as useful instruments for baseline assessment and clinical follow up in patients with IC/BPS in standard clinical practice. These two instruments assess pain (including sexual pain), urinary symptoms and bother/quality of life associated with patients living with IC/BPS, allowing patients to describe their IC/BPS experience. Because of the heterogeneity of patient's clinical presentations, it is likely that the optimal PRO for successful clinical outcomes could be individualized patient PROs based on personal symptoms and goals provided by each patient. The best outcomes will be those that the individual patient desires, not ones developed for all patients.

4.6 | Limitations

The committee recognizes limitations related to individual committee members' personal bias, the inherent lack of outcome reliability studies and the lack of a gold standard comparison for the various outcomes. The methodology did not employ a systematic review and rating of the evidence as required by GRADE (Grading of Recommendations, Assessment, Development and Evaluations) [50] methodology, but rather a comprehensive review and discussion of the literature based on expertise, experience and expert group consensus feedback. The role of cystoscopy, urodynamics, and pain mapping (considered by some as possible non-PRO outcomes) has been addressed by the Diagnosis and Phenotype IC/BPS consensus meeting committees and have not been addressed by this PRO committee. The impact of trial design (inclusion/exclusion criteria) on research outcomes are also beyond the scope of this committee.

5 | Summary

The outcomes committee of the IC/BPS Consensus Meeting believes that more effort must be made to develop and validate a better IC/BPS specific PRO, based on unbiased patient qualitative research methodology, to better delineate outcomes in this enigmatic and variable pain/urinary syndrome. At the present time, the only recommend primary outcome is the NRS/VAS pain scale and voiding diaries as reasonable primary endpoint outcome measures. These are crude outcome measures that do not consider the complexities of the condition, of patients' variable clinical phenotypes and/or patients' desires and expectations. The committee believes that the best available IC/BPS specific secondary PROMs include the patients' subjective assessment of outcomes (GRA) and composite scores of pain, urinary symptoms and impact/quality of life. Arguably the most accepted contemporary composite IC/BPS specific PROM is the NIH GUPI (the OS ICSI/PI can be used for trial comparisons), although further validation and reliability testing of other instruments may result in better and simpler assessment outcome tools. Researchers and physicians managing IC/BPS patients need to be aware and if appropriate, use generic PROMs that measure and describe pain, quality of life, sexual, and psychosocial parameters of this complex biopsychosocial condition. Until a validated PRO that reliably measures change over time is developed, the committee believes that the NIH GUPI or the PUF questionnaire provides reasonable clinical evaluation of patients in standard general practice. Above all, the committee strongly believes that more research is required to create better IC/BPS PRO-based outcome measures.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

B.H.—none; M.N.—none; R.J.E.—Board of Directors for Vaneltix Pharma; S.H.—list; D.J.—Speaker fee, Research Grants, Consultancy for Laborie, IBSA Pharma, Goodlife Pharma BV, Tramedico BV, Glycologix; C.K.—CEO of Interstitial Cystitis Association; S.P.—none; J.C.N.—Consultant for Inmunotek and Redleaf Medical.

Data Availability Statement

Authors commit to making their review article literature search available.

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