ADVISORY COMMITTEE INDUSTRY (URIGEN)
BRIEFING DOCUMENT

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Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC)

Meeting Date: 7 December 2017

Advisory Committee Briefing Material
Urigen Pharmaceuticals, Inc.

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1.0 EXECUTIVE SUMMARY

Interstitial Cystitis / Bladder Pain Syndrome ("IC/BPS") should be considered a single disease that presents with a constellation of symptoms of bladder pain, urinary urgency and frequency. The predominant and most bothersome symptom is pain, which is usually the presenting complaint for patients seeking treatment; however, all the symptoms have varying degrees of presentation. These symptoms can range from mild to severe, and they can be chronic or present as intermittent acute attacks or flares. Diagnosis of IC/BPS is a diagnosis of exclusion once other causes for the observed symptoms have been eliminated, there are no known assessments to better diagnose the condition than from the bothersome symptoms, and there is no current basis on which to separate the patient population into discrete forms of the disease, such as IC versus BPS. Developers of drugs to treat IC/BPS should identify study populations based on patient symptomology and the target indication.

Pain is the hallmark and most bothersome symptom of IC/BPS patients; therefore, trial design and the demonstration of clinical benefit in IC/BPS subjects should focus on treating pain. Pain level should be the main criterion for enrollment, and reduction in pain should be the primary outcome variable. There are multiple validated outcome measures for pain. Demonstration of benefit should require changes in pain scores over time, either acutely or chronically, depending on the target indication, in trials designed to demonstrate the drugs clinical effect over that time line.

IC/BPS is also characterized by urinary urgency and frequency. A reduction in bladder urinary symptoms should provide the basis for secondary endpoints for therapies that target pain. However, because urinary urgency currently has no validated outcome measures, validation of urinary assessments should be performed in the intended patient population and can be the basis for showing efficacy on urinary outcome measures over the short term. Quality of life or global assessments that are based on these urinary symptoms may provide a better efficacy assessment over the longer term than over the short term, because over the short term, subjects may not be bothered by acute urinary symptoms. This is especially true if the global assessment instrument uses evaluation criteria that favors longer term changes.

Accordingly, in general, a new product to treat IC/BPS would be expected to have a statistically significant and clinically meaningful benefit on pain as a primary outcome measure, along with a clinically meaningful benefit on at least one of the urinary symptoms as a secondary outcome measure. Clinical trials should be designed to demonstrate these effects over a timeline appropriate for the therapy's intended effect. However, because of the broad spectrum of symptom severity in IC/BPS patients, and the observation that symptoms do not remain constant over time, there may be strong cases for indications based on outcomes that are more focused on a single symptom. Each therapy should be evaluated independently on its potential to provide a clinically meaningful benefit to patients.

The variable presentation of the disease has contributed to a debate about nomenclature. The IC/BPS designation does not currently refer to different populations of patients with distinct diseases, but rather the two terms have come together to provide a descriptor for a single disease with a constellation of symptoms. While the disease symptoms range from mild to very severe, there is no current test available which can be used to identify a specific separate condition or patient population. Diagnosis based on invasive procedures such as cystoscopy with hydrodistension has not proven to be a reliable test over a symptom-based diagnosis. In fact, invasive hydrodistension procedures themselves are known to affect the symptoms of the disease and are actually used as treatments, further clouding their use a diagnostic procedure. Until better diagnostic criteria become available, IC/BPS remains a disease with a variable nature of clinical presentation that is best identified through symptomatology.

In summary, sponsors developing products to treat IC/BPS should recognize that patients will present with a spectrum of symptoms, and select appropriate populations that will most benefit from the intended treatment. Evaluation of each therapy's intended function, potential treatment effect, route of delivery, and safety should be performed to design outcome measures and trial designs that have the best potential to show a clinically meaningful benefit for the new product. This approach should yield much needed therapies with clear benefits for IC/BPS patients.

2.0 INTRODUCTION

The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) is scheduled to:

> "…discuss appropriate patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome. The committee will also discuss whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions."

Urigen Pharmaceuticals, Inc. is developing three products to treat IC/BPS. Two products that are to be administered by the intravesical route, and the third product is designed to be dosed orally. Urigen is developing products that are expected to be used for the acute management of IC/BPS pain, for chronic management of the condition, and products that have the potential to be disease modifying. This document represents Urigen's rationale and recommendations for the development of such therapies for treatment of IC/BPS patients.

This document provides background information on IC/BPS as a single disease state, its history and diagnosis, as well as proposals for appropriate clinical trial design features and study endpoints for different approaches to treatment, for patients of varying severity of disease.

3.0 INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a disease that was considered rare as recently as 1990. The hallmark symptom of the disease is bladder pain or a form of pelvic pain, typically accompanied by urinary urgency and frequency. Traditionally IC/BPS was diagnosed rarely due to many misdiagnoses such as urinary tract infection in women and prostatitis in men. As knowledge and awareness of the disease and its symptomatology increased, the reported prevalence has increased. In 1990, it was thought that 60,000 to 80,000 women in the US had IC/BPS [Held 1990]. In 1997, it was believed to have increased to 500,000 to one million [Jones 1997]. Individual clinics have shown high rates of prevalence when utilizing a questionnaire that encompasses a more complete battery of IC/BPS symptoms [Parsons 2002, 2004]. More recently the Rand Corporation screened over 100,000 households using symptom questionnaires, and estimated that 3 to 7% of women in the United States over 18 years of age had IC/BPS [Berry 2011], and a similar investigation focused on males estimated a prevalence of 2 to 4% in men [Suskind 2013].

It is now widely accepted that IC/BPS includes many patients with mild, intermittent, and severe forms of disease [Teichman 2007]. For patients with severe disease, living with pain scores of 8 to 10 on an 11-point pain scale, there are limited or no effective treatments available. Many of these patients have a quality of life reported to be worse than dialysis patients and, there have been reported events of suicide [Ratner 2001]. Most patients with IC/BPS have low grade bladder symptoms (3 out of 10) punctuated by intense flares of 8 to 10 that last from 3 days to 3 weeks and may occur infrequently or 5 to 8 times per year. These flares are often incorrectly diagnosed. Diagnosed patients are taught to manage their disease to minimize the bothersome symptoms, but for many undiagnosed patients, living with intermittent pelvic pain and not knowing the source or how to treat it is the norm, as the accompanying symptoms of urinary urgency and frequency have been overlooked as key to the diagnosis of IC/BPS.

These patients are deserving of effective drugs to treat their IC/BPS condition. They are a broad patient population, generally in the prime of their lives, and live with a condition for which there are limited treatment options. There is a clear need to develop new therapies that deliver clinically meaningful relief of pain and show improvements in the urinary symptoms of urgency and frequency and restore quality of life to this patient population.

3.1 History of Research into IC/BPS Disease

The earliest known documentation of a condition of the bladder having symptoms of IC/BPS (pain, urgency and frequency) dates back to 1836 by Joseph Parish in his medical textbook Practical Observations on Strangulated Hernia and Some of the Diseases of the Urinary Organs 2nd edition. In his book, Parrish described a condition that he called “tic doloureux of the bladder” [Parish 1836] that was coined by his mentor Dr. Phillip Syng Physick who had described the condition of

bladder inflammation in the absence of stones as early in 1808. The terms “chronic” and “acute cystitis” of the bladder was introduced in 1855 by Samuel D Gross [Gross 1855] to describe an inflammatory condition of the bladder that begins in the mucous membrane. In the acute form Gross describes a condition where the patient has symptoms of “dull, obscure, deep-seated pain, which rapidly increasing in intensity, soon extends to the neighboring organs”. In addition, Gross states that “the patient now begins to experience frequent calls to void his urine”. “As the disease progresses, the desire to pass water becomes more frequent and urgent, the pain in the bladder assumes a lancinating, tearing or throbbing character”. Gross describes the acute form as infrequent but the chronic form “is sufficiently common, and often entails a vast amount of suffering, which continuing for months and perhaps years”. The condition and symptoms, well described by Gross, are indicative of the hallmarks of IC and that of patients experiencing chronic pain and painful flares.

Gross also described “ulcers of the inflammatory bladder” and in his 3rd edition revised in 1876 by his son Samuel W Gross [Gross 1876], as “the rarest terminations of acute cystitis” and “the most frequent cause of ulceration of the bladder is protracted chronic cystitis”. Also in the 3rd edition Gross first uses the name “Interstitial Cystitis” as a description for “When all the coats are implicated, it is termed interstitial or parenchymatous cystitis . . . When the mucous membrane and submucous connective tissue alone participate in the morbid action, it is known as mucous cystitis, the ordinary form of the disease” [Meijink 2014]. In 1887 Alexander Skene narrowed the term IC to define the progression of acute or chronic inflammation to ulcerations [Skene 1878]. It was after this that IC was used to define ulcers. However, Gross had not used the term in his chapter on bladder ulcerations.

In the following 60 years there was a long succession of names used to describe the condition [O’Connor 1964] including “elusive ulcer” and “Hunner ulcer” named after Guy Leroy Hunner, who described a rare type of bladder ulcer in women [Hunner 1915, 1918]. Over the years the term Hunner’s ulcer or lesion became synonymous with IC leading to often wrongful diagnosis, as many physicians expected to see “ulcers” at cystoscopy, when in fact most of the time true ulcers were not present [Walsh 1978]. Lesion is the more accurate term, because these lesions are covered by epithelium, and hence not true ulcers. Walsh did describe red dots observed by cystoscopy with distension as glomerulations and Messing and Stamey stated that “multiple petechia-like hemorrhages (glomerulations) on the second distention of the bladder is the hallmark of interstitial cystitis and that a reduced bladder capacity and a Hunner's ulcer (sic) represent a different (classic) stage of this disease” [Messing 1978]. In 1988 the National Institute of Diabetes, Digestive and Kidney Diseases (“NIDDK”) adopted the strict requirement that patients must have either glomerulations or classic Hunner’s ulcer (sic) on cystoscopic examination [Gillenwater 1988]. In the 1990’s several researchers found that the NIDDK criteria was overly strict and that there were inconsistencies in the use of cystoscopy as a defining criterion for diagnosis [Meijink 2014]. In

fact, Hanno et.al had determined that the strict NIDDK criteria would have excluded 60% of woman meeting the basic criteria for pain, urgency and frequency to be considered definitely or likely to have interstitial cystitis that were in the large multicenter NIDDK research database [Hanno 1999].

In 2002 Abrams et.al published The Standardisation of Terminology in Lower Urinary Tract Function: Report From The Standardisation Sub-Committee Of The International Continence Society (ICS) that introduced a new terminology Painful Bladder Syndrome (PBS): "PBS is the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology" [Abrams 2002]. Although the ICS preferred the term PBS over IC, the two became combined as IC/PBS or PBS/IC. According to the 2008 Association of Reproductive Health Professionals guidelines on the Diagnosis and Management of Interstitial Cystitis/Painful Bladder Syndrome PBS/IC is defined as "Pelvic pain, pressure, or discomfort related to the bladder, typically associated with persistent urge to void or urinary frequency, in the absence of infection or other pathology" [ARHP 2017]. PBS/IC became a standardized nomenclature and is often still used in publications and guidelines including the most recent NIDDK definition; "Interstitial cystitis (IC), also called bladder pain syndrome, is a chronic, or long-lasting, condition that causes painful urinary symptoms. Symptoms of IC may be different from person to person. For example, some people feel mild discomfort, pressure, or tenderness in the pelvic area. Other people may have intense pain in the bladder or struggle with urinary urgency, the sudden need to urinate, or frequency, the need to urinate more often" [NIDDK 2017].

The latest terminology introduced to describe the condition was developed via consensus by the European Society for the Study of Interstitial Cystitis (ESSIC). In the 2008 article Diagnostic Criteria, Classification, and Nomenclature for Painful Bladder Syndrome/Interstitial Cystitis: An ESSIC Proposal, van de Merwe et.al created the term Bladder Pain Syndrome (BPS) [Van de Merwe 2008]. BPS was meant as a replacement for the name IC believing that the term had become misleading due to multiple meanings across the world. The new term BPS defined the condition as "chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or urinary frequency", although the combined name of BPS/IC would be used during any transition period. In addition, BPS could be further classified into subgroups according to whether cystoscopy with hydrodistension was performed and showed the presence of glomerulations or Hunner's lesions. However, recently Wennevik et.al stated that "there is no consistent relationship between glomerulations and the diagnosis of bladder pain syndrome/interstitial cystitis" [Wennevik 2016]. Oddly enough the original impetus to develop the new terminology by the ESSIC was in response to the early 1988 NIDDK definition and diagnostic criteria that are no longer used today. The term IC/BPS has also been adopted by the American Urological

Association (AUA) in its latest guideline on the diagnosis and treatment of the disease. The current guidelines recommend diagnosis based on symptoms as the initial criteria, only using cystoscopy as an aid to diagnosis for complex presentations [AUA 2014].

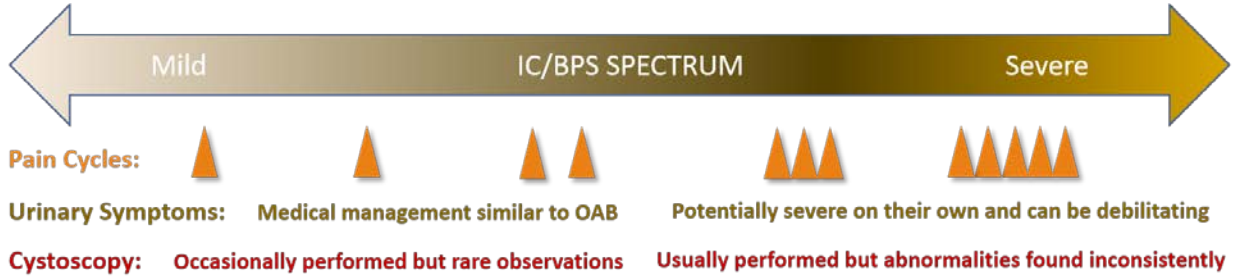
The advent of the term Overactive Bladder (OAB), made popular at the 1997 consensus conference, chaired by Abrams and Wein entitled "The Overactive Bladder: From Basic Science to Clinical Management," [Abrams 1997], and defined OAB as urgency, with or without urge incontinence, usually with frequency and nocturia. It was also published in The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society 2002 [Abrams 2002]. The formalization of OAB as a condition has further confused IC/BPS classification since there is a high degree of overlap between the urgency, frequency and nocturia symptoms associated with both conditions, leaving the hallmark symptom for IC/BPS as pain, which is a clear separator from OAB. The overlap in symptoms is illustrated in Figure 1 and has been implicated in the potential for often underdiagnosing IC/BPS as OAB, especially refractory OAB [Minaglia 2005 and DeLong 2012]. In fact, Chung 2003 tested 98 patients diagnosed with OAB using IC/BPS assessments, including potassium sensitivity, and found that 2/3 diagnosed with OAB also tested positive for the diagnosis of IC/BPS. The symptom overlap suggests that the two diseases may share a common etiology and pathophysiology and that patients diagnosed with severe or refractory OAB should also be evaluated for IC/BPS [Chung 2003, MacDiarmid 2007, DeLong 2012 and Ackerman 2017(2)]

Figure 1: Potential Overlap Between OAB and IC/BPS Symptoms

Fig. 1 Potential relationship between overactive bladder (OAB) and interstitial cystitis/painful bladder syndrome (IC/PBS). UDS, urodynamics (DeLong 2012)

In summary, IC/BPS has been recognized as a disease of the bladder characterized by pain with associated urinary symptoms since the 1800's. It is now recognized that painful episodes of the disease are common, and are very disruptive to patient's lives and associated with great healthcare resource utilization [Sutcliffe MAPP Network 2014, 2015(2)]. The name Interstitial Cystitis was first coined in 1876 by Gross, and since then there have been numerous attempts to rename, reclassify, and ultimately add names to describe the condition. Unfortunately, over the years, IC became synonymous with lesions or ulcers, and this link still persists today with some believing that it should be considered a separate disease from IC/BPS [Fall 2014]. However, there is not strong evidence to support this notion and it is contrary to most evidence including the original writings by Gross. IC and BPS clearly do not represent different diseases and the use of the terms in combination as IC/BPS/PBS has become a standard practice including adoption by the AUA and NIDDK to represent the spectrum of symptom presentation of the disease. Figure 2 provides a potential overview of the disease that might best fit all of the data generated over the years while also maintaining its historical integrity.

Figure 2: The Spectrum of IC/BPS Symptomology

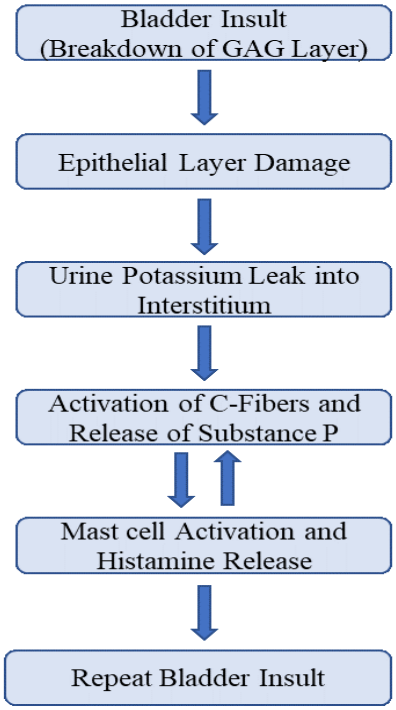


3.2 Pathophysiology

Many researchers agree that IC is a heterogenous disease characterized by bladder pain, with associated urinary urgency and frequency. While there may be more than one contributing factor, the most well characterized mechanism is a dysfunction of the bladder urothelium that leads to leakage of toxins from the urine, in particular potassium, causing depolarization of nerves and muscle, mast cell activation, inflammation and eventual tissue damage [Sant 2007, Chancellor 2004]. The exact mechanism of how the urothelium becomes dysfunctional includes possible insult to the urothelium from bacterial cystitis, childbirth, pelvic surgery or use of urologic instrumentation [Evans, 2005]. Another common belief is that the normal protective mucus coating on the surface of the urothelium becomes damaged allowing direct contact of the bladder wall with urine. The normal protective mucus coating is composed of glycosaminoglycans (GAG),

multifunctional mucopolysaccharides that bind covalently to a protein core to form a proteoglycan molecule that is hydrophilic and traps water at the outer layer of the umbrella cell [Parsons 2011 and Keay 2014]. This trapped water forms a barrier at the critical interface between urine and the bladder. The result is a highly impermeable urothelium that serves as a key protective barrier [Parsons 2007]. Loss of the protective GAG layer allows urine to contact the bladder wall carrying toxic solutes (potassium) that causes damage to the urothelium. The diffusion of excess potassium into the bladder interstitium through a defective urothelium triggers neuronal and muscle cell trauma through depolarization, and mast cell activation [Sant 2007 and Parsons 2011]. While the damage to neurons and muscles might be transient, the activation of the mast cells results in a cycle of neuronal hyperexcitability leading to secretion of neurotransmitters and triggering further mast cell stimulation and degranulation. This process appears to contribute to the chronic pain, urgency, and frequency experienced by patients [Sant 2007 and Grover 2011]. Figure 3 highlights the cascade of events that lead to IC/BPS.

Figure 3: IC/BPS Event Cascade



Adapted from Evans. Treatment approaches for interstial cystitis: multimodal therapy. Rev Urol. 2002; 4(suppl 1): 16-20

Researchers have also looked at the genetics and genomics of IC/BPS to better understand the molecular and phenotypic characteristics of the disease. Several studies have suggested that there is a genetic correlation to IC/BPS and that immediate family members have a higher probability of displaying symptoms of IC/BPS if there is already a family member diagnosed with the disease [Dimitrakov 2001, Warren 2004 and Parsons 2015]. Genomic expression profiling has shown extensive promise in elucidating the genes that might be involved in the etiology of the disease and offers possible directions for non-invasive diagnostics. Several researchers have looked at micro-array analysis of a few to over several hundred genes from both bladder biopsies and urine of IC/BPS patients [Tseng 2009, 2010, Blalock 2012 and Colaco 2014]. Results of these studies suggest potential genes that are up-regulated in bladder tissue of IC/BPS patients and that increased expression of pro inflammatory genes are more prevalent as the disease progresses including possible link to medical findings. These newer technologies may prove useful to identify a source of the disease process and offer novel ways to differentiate patient populations for analysis and treatment, but these technologies are in very early stages and not near validation for current use to better categorize IC/BPS patient population.

3.3 Current Diagnosis Review

The diagnosis of IC/BPS remains one of exclusion, because symptoms of IC/BPS may be similar to other disorders of the bladder. There is also no single validated test that unequivocally identifies or categorizes the disease. According to the AUA Guidelines, the initial diagnosis of the disease should include a thorough history, physical examination and laboratory tests to exclude other disorders and then document symptoms that align with IC/BPS. Other tests such as urodynamics, cystoscopy and biopsy may be used to help rule out other diseases in more complicated cases. The 1988 NIDDK criteria and need for cystoscopic findings have not been updated; however current NIDDK publications [NIH 2011] and the current NIDDK website (https://www.niddk.nih.gov/health-information/urologic-diseases/interstitial-cystitis-painful-bladder-syndrome/diagnosis) are more in line with the AUA, that cystoscopy may be undertaken as part of the diagnostic regimen, not that it would be required. Furthermore, even the nomenclature currently used at NIDDK uses a term similar to IC/BPS, as they refer to it as Interstitial Cystitis (Painful Bladder Syndrome).

The current AUA and NIDDK guidelines are summarized below and the AUA algorithm for diagnosis and treatment is shown in Appendix 1 [AUA 2014 and NIH 2011]. In these documents both organizations use pain of bladder origin as the primary diagnosis with urinary conditions as secondary. Also, both organizations have removed the requirement for visual observation of bladder wall defects such as glomerulations or lesions, via cystoscopy, as a diagnostic requirement, instead recommending cystoscopy only as a test to rule out other conditions as needed.

INTERSTITIAL CYSTITIS / PAINFUL BLADDER SYNDROME [NIDDK Information Clearing house, 2011]

How is IC/PBS (sic) diagnosed?

Because symptoms are similar to those of other disorders of the bladder and there is no definitive test to identify IC/PBS, doctors must rule out other treatable conditions before considering a diagnosis of IC/PBS. The most common of these diseases in both sexes are urinary tract infections and bladder cancer. In men, common diseases include chronic prostatitis or chronic pelvic pain syndrome. In women, endometriosis is a common cause of pelvic pain. IC/PBS is not associated with any increased risk of developing cancer.

The diagnosis of IC/PBS in the general population is based on the

- presence of pain related to the bladder, usually accompanied by frequency and urgency of urination
- absence of other diseases that could cause the symptoms

Diagnostic tests that help rule out other diseases include urinalysis, urine culture, cystoscopy, biopsy of the bladder wall and urethra, and distention of the bladder under anesthesia.

DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME ("AUA Guideline") [AUA, 2014]

Symptoms. Pain (including sensations of pressure and discomfort) is the hallmark symptom of IC/BPS. Typical IC/BPS patients report not only suprapubic pain (or pressure, discomfort) related to bladder filling but pain throughout the pelvis—in the urethra, vulva, vagina, rectum—and in extragenital locations such as the lower abdomen and back. The prototypical IC/BPS patient also may present with marked urinary urgency and frequency but because these symptoms may indicate other disorders, they do not exclusively indicate the presence of IC/BPS.

Diagnostic Guideline Statements:

Guideline Statement 1.

The basic assessment should include a careful history, physical examination, and laboratory examination to document symptoms and signs that characterize IC/BPS and exclude other disorders that could be the cause of the patient's symptoms. *Clinical Principle*

Guideline Statement 2.

Baseline voiding symptoms and pain levels should be obtained in order to measure subsequent treatment effects. *Clinical Principle*

Guideline Statement 3.

Cystoscopy and/or urodynamics should be considered when the diagnosis is in doubt; these tests are not necessary for making the diagnosis in uncomplicated presentations. *Expert Opinion*

The AUA treatment algorithm is shown in Appendix 1.

3.4 Role of Cystoscopy

The preponderance of evidence shows that cystoscopy with hydrodistension is not a reliable diagnostic tool to positively establish IC/PBS; diagnosis based on symptoms and history is more reliable. There may be a role for cystoscopy to exclude other possible diagnoses in patients whose history and symptoms are inconclusive, and in those cases cystoscopy under local anesthesia may suffice. Despite the lack of supportive evidence, some still consider cystoscopy with hydrodistension an important diagnostic test for IC/PBS [Hand 1949, Messing 1978 and Gillenwater 1987]. The purported positive findings believed to be diagnostic for IC/PBS during the procedure are: Hunner lesions, glomerulations and/or or reduced anesthetic capacity.

Hunner lesions are rare and reported in 5-11% of patients ultimately diagnosed with interstitial cystitis [Nigro 1997, Ottem 2005 and Parsons 1990]. Hunner lesions cannot be readily diagnosed on awake (local anesthesia) cystoscopy [Doiron 2016]. The requirement for anesthesia and hydrodistension arises as there can be misdiagnoses of Hunner lesion as other lesions, such as biopsy scar [Parsons, 1996]. The absence of a Hunner lesion does not preclude the diagnosis of IC/PBS. They are more common in older patients than the typical younger patient [Doiron 2016, Jonat 2011]. Thus, the index IC/PBS patient does not have a Hunner lesion.

Glomerulations are more commonly seen but their presence or absence is also variable [Wennevik 2016]. They are present in approximately 60-80% of patients in most modern series with their presence being reported in as few as 30% of patients [Lokeshwar 2006, Denson 2000 and Standfor 2006]. Again, misinterpretation of glomerulations is also possible as they may have arisen from cystoscope trauma, or the trauma of hydrodistension [Parsons, 1996]. They have been reported to be equally present in both IC patients and asymptomatic controls [Waxman 1998]. There is poor correlation between glomerulation severity and symptoms [Ottem 2005, Doiron 2016 and Wennevik 2016]. Approximately 40-50% of patients have either no glomerulations or scant glomerulations [Ottem 2005 and Denson 2000]. Severe glomerulations (> 5 glomerulations per cystoscopy field and diffusely present across fields with the scope held 1 cm from the epithelium) are generally seen in Hunner lesion cases [Ottem 2005, Doiron 2016]. Interrater reliability is poor [Denson 2000]. Glomerulations may evolve over time [Hand 1949, Shear 2006]. Glomerulation grade does not correlate with improvement to hydrodistension [Ottem 2005]. The absence of glomerulations does not preclude the diagnosis of IC/PBS.

Reduced anesthetic capacity is considered a feature of IC/BPS [Gillenwater 1987]. Reduced anesthetic capacity is thought to correlate with symptom severity. There are few studies that compare anesthetic capacity in IC/BPS patients versus controls. However, two such studies show no difference in anesthetic capacity between IC/BPS and controls [Denson 2000 and Jiang 2016]. Symptoms with reduced capacity and absence of glomerulations or ulcer may present with similar clinical picture [Award 1992]. Hydrodistension volumes do not correlate with voided volumes or symptom response [Ottem 2005, Wennevik 2016 and Payne 2002]. Hydrodistension volumes do correlate with severity of glomerulation grade [Denson 2000].

Use of cystoscopy with hydrodistension under anesthesia as a diagnostic tool is further clouded by the therapeutic effect of the hydrodistension procedure. The procedure is actually recognized as a treatment and listed as a third line treatment in the AUA Guidelines.

In summary, the value of cystoscopy with hydrodistension as a diagnostic tool is low both in terms of positive and negative predictive value. The bulk of data shows that and the markers used (Hunner lesion, glomerulations, anesthetic capacity) have variable presence and variable correlation with symptoms. As a result, the requirement for cystoscopy findings is not warranted in the diagnosis of IC/BPS. The main value of cystoscopy with hydrodistension seems to be to exclude other disease processes and offer potential therapeutic relief [Messing 1978, Ottem 2005 and Award 1992].

4.0 CONSIDERATIONS FOR DESIGN OF CLINICAL TRIAL FOR TREATMENT OF IC/BPS

4.1 Patient Selection Criteria

When discussing the selection criteria for entry into a trial evaluating interventions for the treatment of IC/BPS, one should consider that the main defining hallmark of the disease is bladder pain and this should be the primary endpoint for drug development. Both long term relief of chronic pain and acute relief of painful short duration spikes (flares) are appropriate goals of treatment; different interventions may target either goal. Studies evaluating long-term relief of chronic bladder pain should target the change in painful symptoms from baseline to trial completion, typically at least 12 weeks for a chronic therapy. To account for fluctuation in pain levels over the short term, frequent pain measurements, weekly or daily, may be required. Secondary outcomes could include changes in voiding frequency, urgency and a global response assessment. Studies evaluating treatment of bladder pain associated with flares or acute pain should have as the primary endpoint a reduction in pain from baseline over the course of hours or days. Voiding frequency, urgency or a global response assessment may be appropriate secondary endpoints; however, a short-term therapy may not be expected to show an improvement on a global measure. Based on the desired outcomes the following selection criteria are a generalized list that should be considered for both chronic and acute treatment with notes indicating possible deviations.

4.1.1 Study Inclusion Criteria (based on pain as primary endpoint)

Overall, the inclusion criteria for IC/BPS studies should recognize the broad patient population that is available for enrollment in clinical studies, and enrollment criteria should be selected that define a population appropriate for the therapy being developed. Major considerations for patient selection are defined below, although additional inclusion criteria may be warranted depending on type of intervention or study duration.

Sex

- IC/BPS is much more prevalent in females than in males, by some estimates up to 90% of the patients are female [AUA 2014]. This fact can make it very difficult to enroll male patients if the patient selection criteria are sufficiently tight and the overall numbers of patients intended for the study sufficiently small. The pentosan polysulfate studies enrolled a patient population that was 97% female [Parsons, 1993], and many studies currently underway are enrolling only women. By definition, any IC/BPS program will enroll predominantly women.

- Therefore, there should be no expectation of a minimum number of men enrolled in a IC/BPS clinical development program, and in certain cases it would be appropriate to enroll only women.

Age:

- There do not seem to be any restrictions on age for subjects enrolled in IC/BPS studies.

IC/BPS Diagnosis:

- Have had a previous diagnosis of IC/BPS as per current NIDDK/AUA guidelines (reviewed in this briefing document)
- May or may not have received a cystoscopy in association with their diagnosis of interstitial cystitis/bladder pain syndrome prior to or at time of screening.

Pain:

- Patients should be enrolled based primarily on pain criteria specific for the drug being studied, but the pain scores used should be taken from a validated scale deemed appropriate for the trial. Thus, criteria dynamics could include the following:
    - Duration / history of pain
    - Severity of pain
    - Numbers of episodes of pain of a specific severity
- The actual pain scores used would be taken on validated VANRS scale deemed appropriate for trial.

Urinary Symptoms:

- The same principles of symptom presentation should also apply to the urinary symptoms required for enrollment, and the urinary enrollment criteria may or may not include symptoms of both frequency and urgency, or even a quality of life assessment or global based on urinary symptoms, as appropriate for specific trial).
    - Duration / history of symptoms
    - Severity of symptoms
    - Numbers of episodes of symptoms of a specific severity

Given the variability of symptomology, the urinary symptoms, quality of life, or global assessments used for the trial entry criteria do not need not be included in the outcome assessments, and therefore would not need to be validated. The enrollment assessments may be used to ensure enrolling patients who have a specific severity of disease and to ensure enrollment of a more homogenous population. If an enrollment assessment is also used as an efficacy assessment, then it would need to be validated for the specific outcome in the population enrolled.

4.1.2 Study Exclusion Criteria

Diagnosis of IC/BPS is a diagnosis of exclusion, so many of the exclusion criteria that should be included in a clinical trial of IC/BPS subjects would overlap the exclusions made in the diagnosis of the disease; many of the NIDDK exclusion criteria would apply and can be included in the trial exclusion criteria. This list follows and additional exclusion criteria may be warranted depending on type of intervention or study duration.

- Be positive or recently positive for bacterial infection of the urinary tract
- Neurologic disease affecting bladder function; any previous surgery or procedure having affected bladder function
- Have pain or a pain disorder that, in the opinion of the investigator, would make it difficult to discriminate pelvic pain of bladder origin from the other pain, including but not limited to vulvodynia, vulvar vestibulitis, irritable bowel syndrome, fibromyalgia, central pain sensitivity, active endometriosis or active inflammatory bowel disease
- Have had any of the following:
    - History of pelvic irradiation or radiation cystitis
    - History or presence of uterine, cervical, pelvic, rectal, ovarian or vaginal cancer
    - History of benign or malignant bladder tumors
    - History or presence of tuberculous cystitis
    - History or presence of chemical cystitis, including that due to cyclophosphamide
    - History or presence of urinary schistosomiasis
    - Bladder or ureteral calculi
    - Clinically significant infectious vaginitis
    - Currently uncontrolled genital herpes
    - History or presence of urethral diverticulum
    - Presence of bladder fistulae
    - History of ketamine use

4.2 Endpoints and assessments

4.2.1 Summary of Assessments used for IC/BPS

As pain is the most bothersome symptom and the one that drives patients to seek care, pain should be the primary outcome measure in the clinical evaluation of drugs to treat IC/BPS. Treatments for IC/BPS should also have a clinically meaningful effect on urinary urgency or urinary frequency, or a global assessment, which measures quality of life assessments based on urinary symptoms, can also be used. The decision between a symptom based assessment and a global

assessment may rely upon the duration of treatment. A short-term treatment may not reliably affect a global assessment designed for longer term effect. For a small subset of patients with atypical presentations or particularly severe urinary symptoms, it should be possible to consider therapies for which pain is not the primary outcome.

4.2.2 Pain

There are many validated pain scales that have been used in the development of therapeutics, and the most common are the Visual Analog Numerical Rating Scales (VANRS). The VANRS scales remain appropriate for the study of IC/BPS and have been used in the past [Parsons 2005, 2012 and Nickel, 2016]. However, a key attribute of IC/BPS pain is that it changes over time, with many factors such as bladder filling, menstrual activity, diet, allergies, sexual activity, and others affecting the pain state.

Regression to the mean and high placebo response has been the result of this natural variation in the pain state in studies to treat IC/BPS. It has been noted that the original pentosan polysulfate study population had a placebo response rate of 15%, and that this is now felt to be an unusually low number, due to the fact that the patients entering the study had severe, chronic IC/BPS symptoms. Recent studies have reported placebo response rates of over 20% and over 30%, as better diagnosis has yielded enrollment of patients with more moderate and intermittent IC/BPS symptoms [Parsons 2012, Nickel 2016, Clintrial.gov 2013]. Given that there will be a natural variability in the pain state, the key to successful development of drugs to treat IC/BPS will be the development of strategies to collect and analyze pain data in such a way to show that the drug is having the intended effect.

Products that are expected to work acutely should therefore focus on short term improvements in pain. For example, successful results have recently been published in a study that looked at the reduction in pain from an anesthetic dose over a period of 12 hours [Parsons 2012]. For a product that was expected to show an effect over weeks, another study looked at the change in pain recorded in daily pain diaries over several weeks [Nickel 2016].

Sponsors will need to evaluate the nature of their therapeutic agent and its expected magnitude and time course of effect, and design a pain score and the appropriate statistical analyses that best matches the expected effects of the drug. Products with an effect over the short term can focus on short term amelioration of pain, and products designed to work longer or having a longer lead time to show an effect will be studied over the longer term.

Use of the VANRS for pain assessment in IC/BPS Trials

The VANRS should form the cornerstone of pain management supported by appropriate statistical analyses designed for the therapeutic in question. Other scales could be considered with

justification for cases in which the VANRS may not be appropriate, such as any instance in which the subject would have trouble providing the necessary information. A description of the VANRS follows:

Visual Analog / Numerical Rating Scale (VANRS) for pain

The 11-point VANRS pain scale is a scale that is used to assess bladder pain. The subject is presented a horizontal scale marked from 0 (none) to 10 (worst ever) and is asked to circle the number, from 0 to 10, that best describes the symptom the subject is feeling "right now."

While the statistical treatment of the pain data will likely vary considerably among different treatment modalities, it is expected that the VANRS will remain the core of pain assessments for the IC/BPS population.

4.2.3 Frequency

Bladder Diaries

Bladder diaries are used to support collection of data required for any claim of a reduction in urinary frequency. As urinary frequency is a recognized symptom of IC/BPS it would be expected that IC/BPS patients being studied in a clinical trial should keep some sort of voiding log during the study, even if the data is not being used to support a claim.

4.2.4 Urgency

There are no published validated scales for the assessment of urinary urgency in an IC/BPS trial, so any scales that a sponsor would employ still require validation. Development of a validated scale would be a valuable instrument for future studies.

Like pain, the urgency experienced by an IC/BPS patient may not be static and may vary over time. This will need to be evaluated by the sponsor for the expected time course of the treatment.

A description of some urgency scales that have been described follows:

Patient Perception of Intensity of Urgency Scale (PPIUS) [Mathias 2014]:

The PPIUS is a modified micturition diary into which patients enter each micturition, accompanied by descriptive information about the urgency of the void. It includes an indication of whether the void was into a toilet or an episode of incontinence or urge incontinence, and the urgency severity of the void is given a value on a 5-point scale (0 to 4)

Visual Analog / Numerical Rating Scale (VANRS) for urgency [Parsons 2012]:

The 11-point VANRS urgency scale is a scale, similar to the VANRS for pain, that is used to assess urinary urgency. The subject is presented a horizontal scale marked from 0 (none) to 10

(worst ever) and is asked to circle the number, from 0 to 10, that best describes the symptom the subject is feeling "right now."

A six-point VANRS urgency scale was used in a double-blind placebo controlled multisite study on pentosan polysulfate, which demonstrated significant improvement over placebo [Parsons 1993].

4.2.5 Global Assessments

Numerous Assessments have been used in the development of therapies for the treatment of IC/BPS or for the assessment of patients with the condition. These include the following non-exhaustive list, which shows both assessments which focus only on the global assessment, and others which include symptom assessment in combination with a global assessment, and others which go further and try to determine what is the bothersome nature of the symptoms. As has been noted previously, it may be appropriate for global assessment to apply to longer term treatments as short-term treatments may not show an effect on a global assessment with questions focused on the longer term.

Global Response Assessment (GRA)

The GRA is a scale that measures overall improvement with therapy. The assessment asks: "As compared to when you started the study [treatment], how would you rate your interstitial cystitis symptoms now?"

The 7-point scale is centered at zero (no change): markedly worse; moderately worse; slightly worse; no change; slightly improved; moderately improved; and markedly improved.

This scale was used in a double-blind placebo controlled multisite study on pentosan polysulfate which demonstrated significant improvement over placebo [Parsons 1993].

Overactive Bladder Questionnaire (OAB-q) [Coyne 2014]:

The OAB-q has been validated for use in the OAB patient population. It includes a series of 4 questions about bothersome urinary urgency questions, and a further 12 questions dealing with more general quality of life issues, on a 6-point scale as follows: Not at all; A little bit; Somewhat; Quite a bit; A great deal; and A very great deal.

Patient Perception of Bladder Condition (PPBC) [Coyne 2006]:

The PPBC is a global assessment scale that assesses bladder condition. The assessment asks: "what statement best describes your bladder condition".

The 6-answer scale has the following possible responses: My bladder condition does not cause me any problems at all; My bladder condition causes me some very minor problems; My bladder

condition causes me some minor problems; My bladder condition causes me (some) moderate problems; My bladder condition causes me severe problems; and My bladder condition causes me many severe problems.

Benefit, Satisfaction and Willingness to Continue (BSWC) questionnaire [Pleil 2005]:

The BSWC is a patient global assessment survey that is not specific to urology as it has been used in several therapeutic areas.

It seeks information on the perception of benefit of the treatment, the satisfaction, and the willingness to continue, and following a yes or no response digs deeper with another binary check on whether the yes/no response was very emphatic or not.

Visual Analog / Numerical Rating Scale (VANRS) for treatment satisfaction:

The 11-point VANRS treatment satisfaction scale is a scale that are used to assess treatment satisfaction. The subject is presented a horizontal scale marked from 0 (none) to 10 (totally satisfied) and is asked to circle the number, from 0 to 10, that best describes the satisfaction the subject feels he has received from the treatment.

Combined Symptom/Symptom bother

Pelvic Pain and Urgency/Frequency (PUF) questionnaire [Parsons 2002]:

The PUF questionnaire is a series of 8 questions, some broken into parts, a symptom score and a bother score. The PUF questionnaire attempts to both generate information on symptoms, and how bothersome the symptoms are for the patients. It is scored on a scale from 0-3 or 0-4 for each question, and includes three questions on frequency, three on urgency and two on sexually associated symptoms and hence is a comprehensive evaluation of many IC/BPS symptoms.

O/Leary Sant Voiding and Pain Indices (OLS) [O'Leary 1997]:

The OLS questionnaire attempts to both determine symptom score and to evaluate how bothersome are the symptoms.

The questionnaire asks 4 questions on symptoms related to pain, urgency, frequency and nocturia, and generates both a symptom value and value for associated bother. The qualitative responses range from few symptoms and no problem through to major symptoms and big problem, on a 5- or 6-point scale.

Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) [Humphrey 2011]:

The BPIC-SS questionnaire was developed as an assessment tool for determining patient's eligibility for entrance into a clinical trial. It may be well suited for identifying moderate to severe

patients. The assessment may also be utilized as an outcome measurement. The assessment consists of 8 questions evaluating pain, frequency and urgency associated with IC/BPS

Patient Overall Rating of Improvement of Symptoms (PORIS) questionnaire [Parsons 1993]:

The PORIS questionnaire comprises three questions that ask the subject to report the overall change in pain and urgency now as compared with before study drug administration. The choices are the same for each symptom: worse, no better (0% improvement), slightly improved (25% improvement), moderately improved (50% improvement), greatly improved (75% improvement), and symptoms gone (100% improvement). The third question is global and simply asks the subject to report overall change.

Refer to Appendix 2 for examples of the assessment questionnaires

5.0 CONCLUSIONS

IC/BPS is a single disease with a variable presentation of symptoms of pain, urinary urgency and urinary frequency.

As pain is the most bothersome symptom and the one that drives patients to seek treatment, pain should be the primary patient selection criteria and the primary outcome measure in any clinical program to develop a drug for treatment of IC/BPS. A secondary symptom such as urinary urgency or frequency should also show clinically meaningful benefit. Global and quality of life assessments are important but may best show effect for therapies intended to have an effect over the longer duration.

Sponsors should consider the therapeutic effect, route of delivery, and safety profile of their proposed drug candidate, and make decisions regarding the patient profile most likely to benefit from it. If the effect of the drug is short term, then patients can be enrolled who have short term pain and outcome measurements can be those that provide the most benefit over the short term in trials of short duration. If the symptoms, especially pain, are severe, more invasive treatment regimens, or those with greater risks could be justified. Products intended to work over the long term or that have a more gradual effect, need to be studied over timelines sufficient to observe their effect.

The most effective way to show efficacy in reasonable numbers of patients would be to compare the changes in pain over an appropriate period of time. Because in IC/BPS patients, their pain statuses wax and wane over time, it is likely necessary to develop pain scales that take this variability into account. Snapshots of pain at defined timepoints should be included as a secondary outcome analysis.

There are many validated pain scales and the most common is the Visual Analog Numerical Rating Scale (VANRS). While the statistical treatment of the pain data will likely vary considerably among different treatment modalities, it is expected that the VANRS will remain the core of pain assessments for the IC/BPS population. Other scales could be considered with justification.

Treatments for pain in IC/BPS should also have a clinically meaningful effect on urinary urgency or urinary frequency. Where appropriate for the sensitivity of the measurement, global assessments or quality of life assessments can be used. For short term treatments, that affect urinary frequency, the assessment would be straightforward, comparing the number of voids over time. Urinary urgency could also be readily assessed in a short-term study, although there are no validated urgency assessments known for use in the IC/BPS population. In the absence of a universal accepted validated scale for urgency, sponsors should be responsible to develop and validate scales for their specific population and expected benefit. The urinary outcome measurements should be secondary outcome measures for therapies with a primary effect on pain.

For global outcome measures and quality of life measurements, there have been many developed for the IC/BPS population. The long list of those that has been used shows that clinical researchers feel this outcome measure is important as they evaluate different treatments for IC/BPS, but also that no single established assessment exists. Many of them are similar in nature focused on whether the patient or the physician believes the patient has seen an improvement in their condition. Another line of assessment attempts to understand how bothersome the symptoms are. Sponsors will need to evaluate the expected effect of the drug under development, and decide which assessment is best to show the drugs effect. The 7-point improvement scales and the bothersome symptom scales, seem to be logical choices to validate and begin using by consensus for the clinical study of IC/BPS. For short term treatments, it may not be possible to properly assess quality of life or global improvements, so they may rely on demonstrating a reduction in urinary symptoms.

The patient symptomology is the best way to define a study population; there are no currently available tests, that can better define the patient population. Sponsors should enroll patients into studies with symptoms that their product has the best chance of addressing. The study assessments should focus on pain as a primary outcome measure, for which a VASNRS scale is likely appropriate, but statistical treatment will depend on the duration of therapy and intended treatment effect. A secondary symptom such as urinary urgency or frequency should also show clinically meaningful benefit. Global and quality of life assessments are important but may best show effect for therapies intended to have an effect over the longer duration. Dependent on allowances for the drugs intended treatment effect and duration, these patient selection criteria and assessment considerations should be considered sufficient for the development of therapies for the treatment of patients with the IC/BPS condition, and can be tailored for the intended treatment populations severity of disease.

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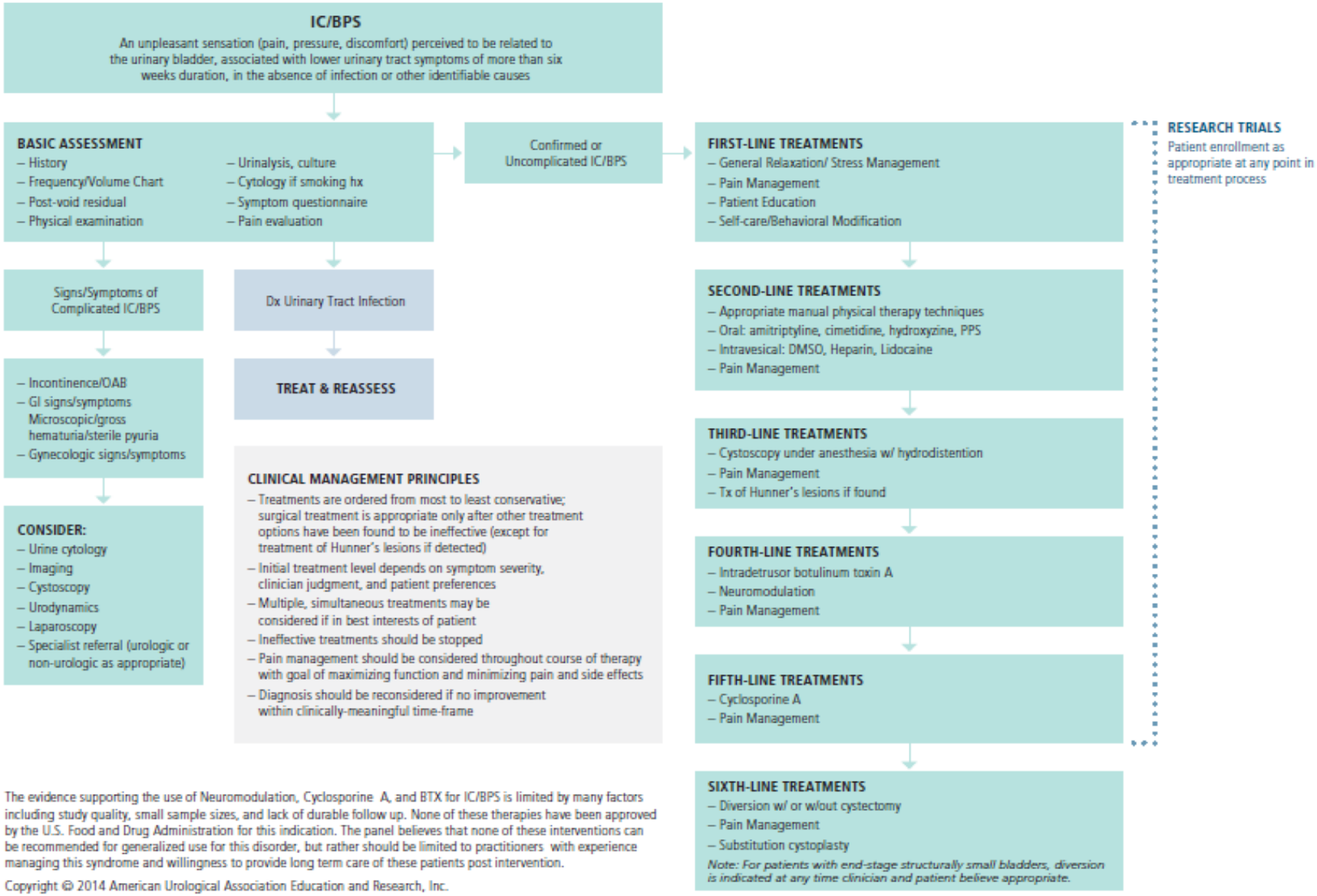
7.0 APPENDICES

Appendix 1: AUA Guideline IC/BPS Diagnosis and Treatment Algorithm



The evidence supporting the use of Neuromodulation, Cyclosporine A, and BTX for IC/BPS is limited by many factors including study quality, small sample sizes, and lack of durable follow up. None of these therapies have been approved by the U.S. Food and Drug Administration for this indication. The panel believes that none of these interventions can be recommended for generalized use for this disorder, but rather should be limited to practitioners with experience managing this syndrome and willingness to provide long term care of these patients post intervention.

Appendix 2: Examples of the Assessment Questionnaires

VANRS for Pain and Urgency – 11 Point Visual Analog Scale for Pain and Urgency

PPIUS – Patient Perception of Intensity of Urgency Scale

GRA – Global Response Assessment

OABq Short Form – Over Active Bladder Questionnaire

PPBC – Patient Perception of Bladder Condition

BSWC – Benefit, Satisfaction and Willingness to Continue Questionnaire

VAS for Treatment Satisfaction – 11 Point Visual Analog Scale for Treatment Satisfaction

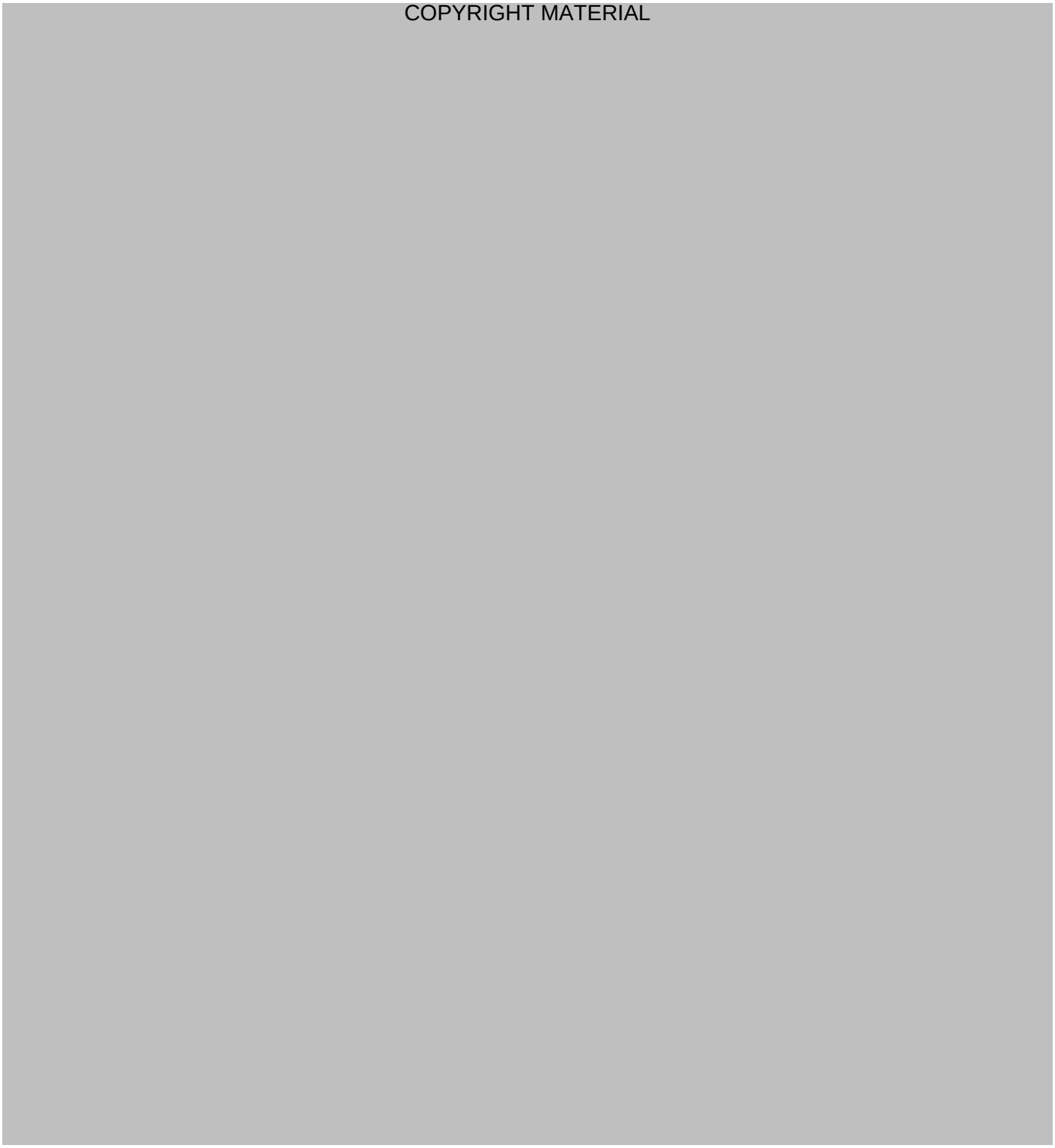
PUF – Pelvic Pain and Urgency Urinary Frequency Questionnaire

OLS – O'Leary/Sant Voiding and Pain Indices

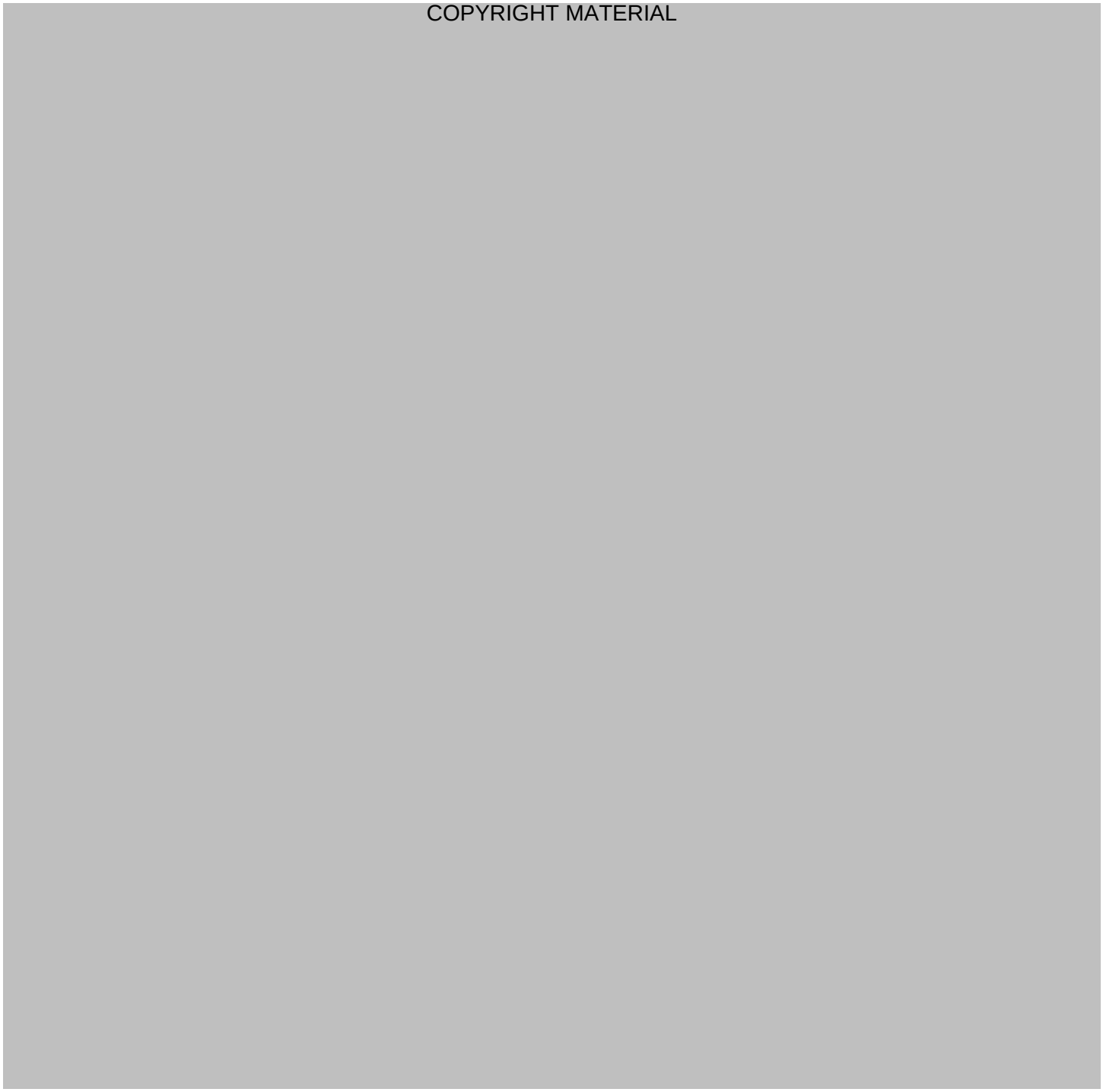
BPIC-SS – Bladder Pain Interstitial Cystitis Symptom Score

PORIS – Patient Overall Rating of Improvement in Symptoms Questionnaire

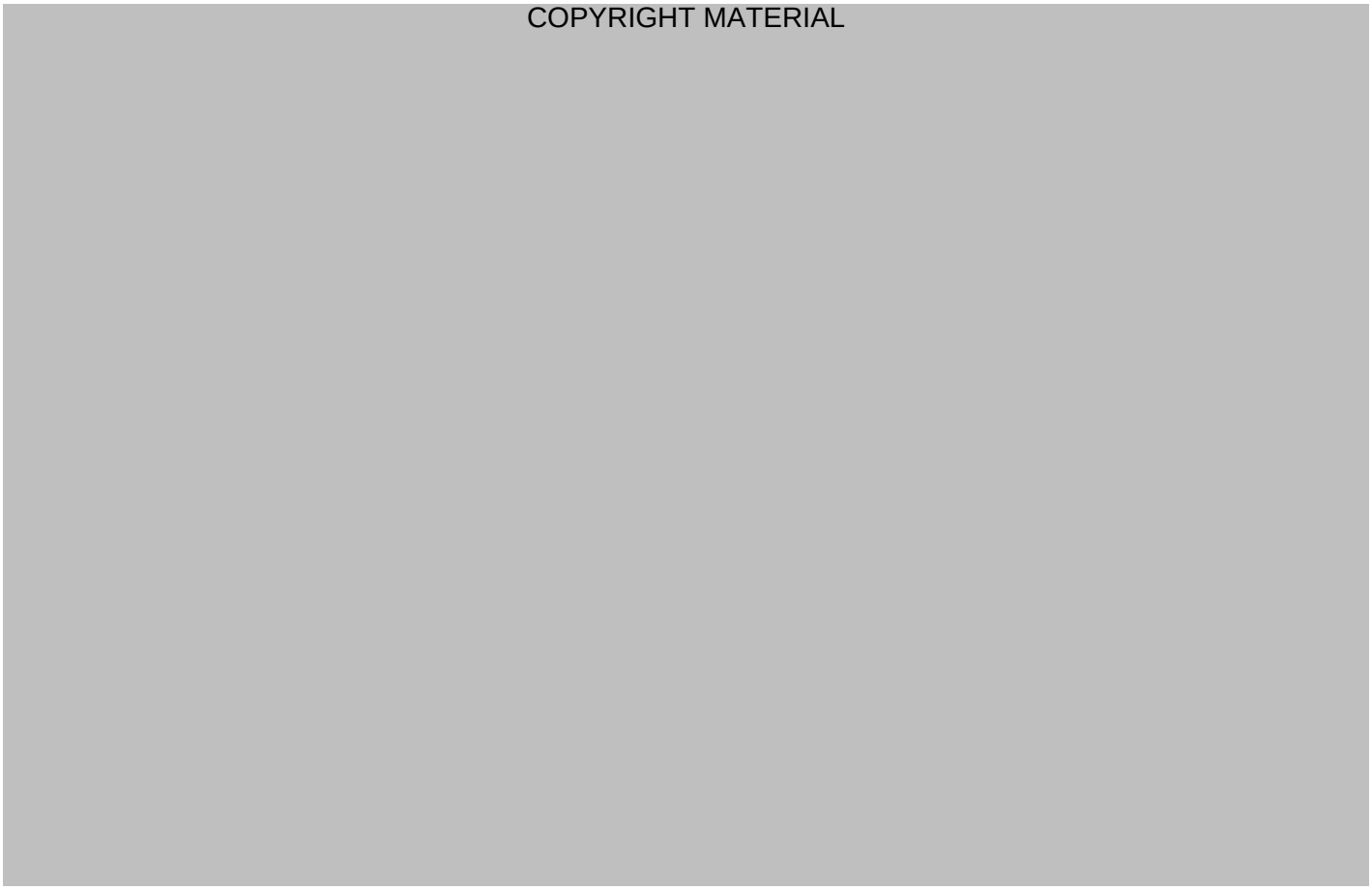
VAS for Pain and Urgency – 11 Point Visual Analog Scale for Pain and Urgency



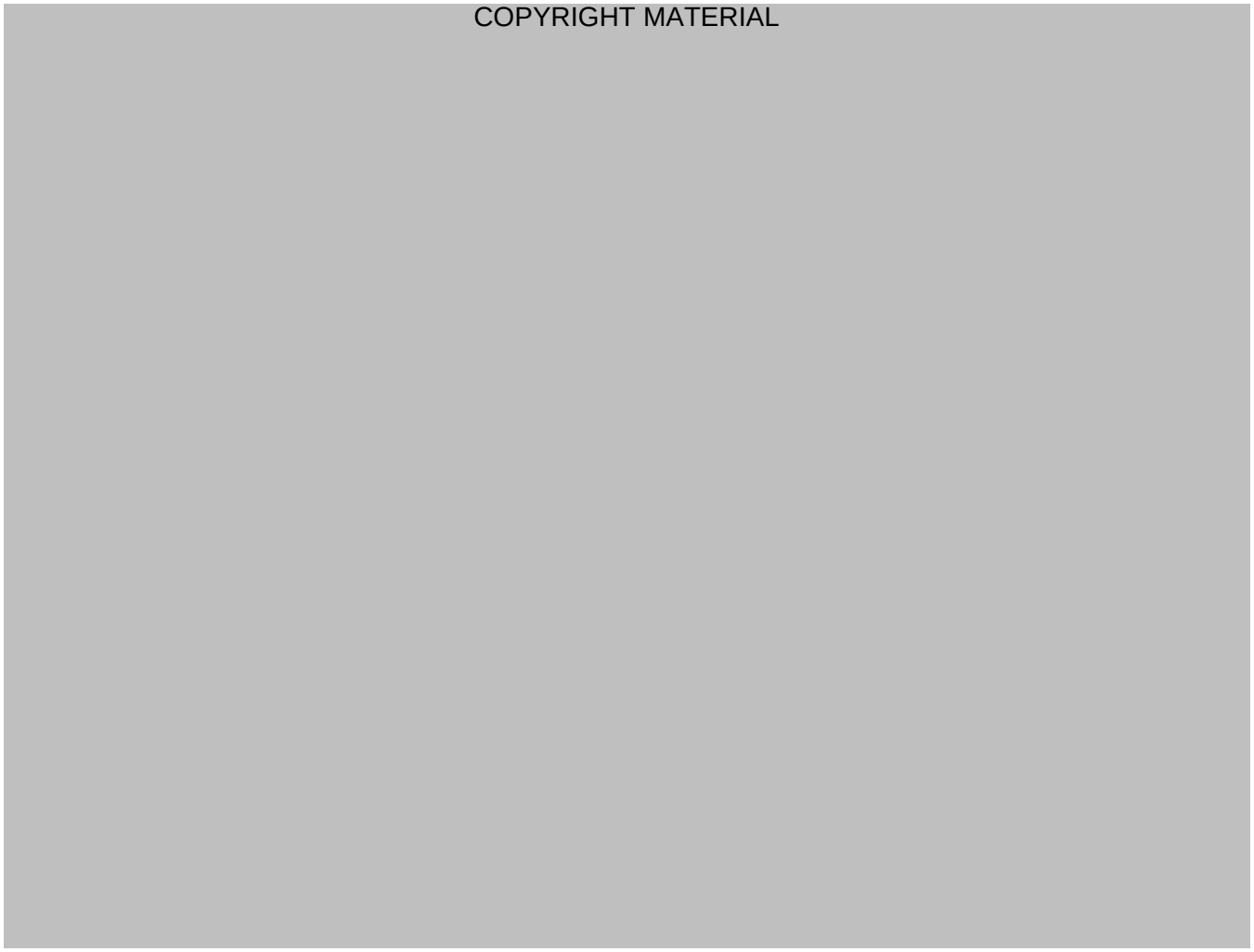
PPIUS – Patient Perception of Intensity of Urgency Scale



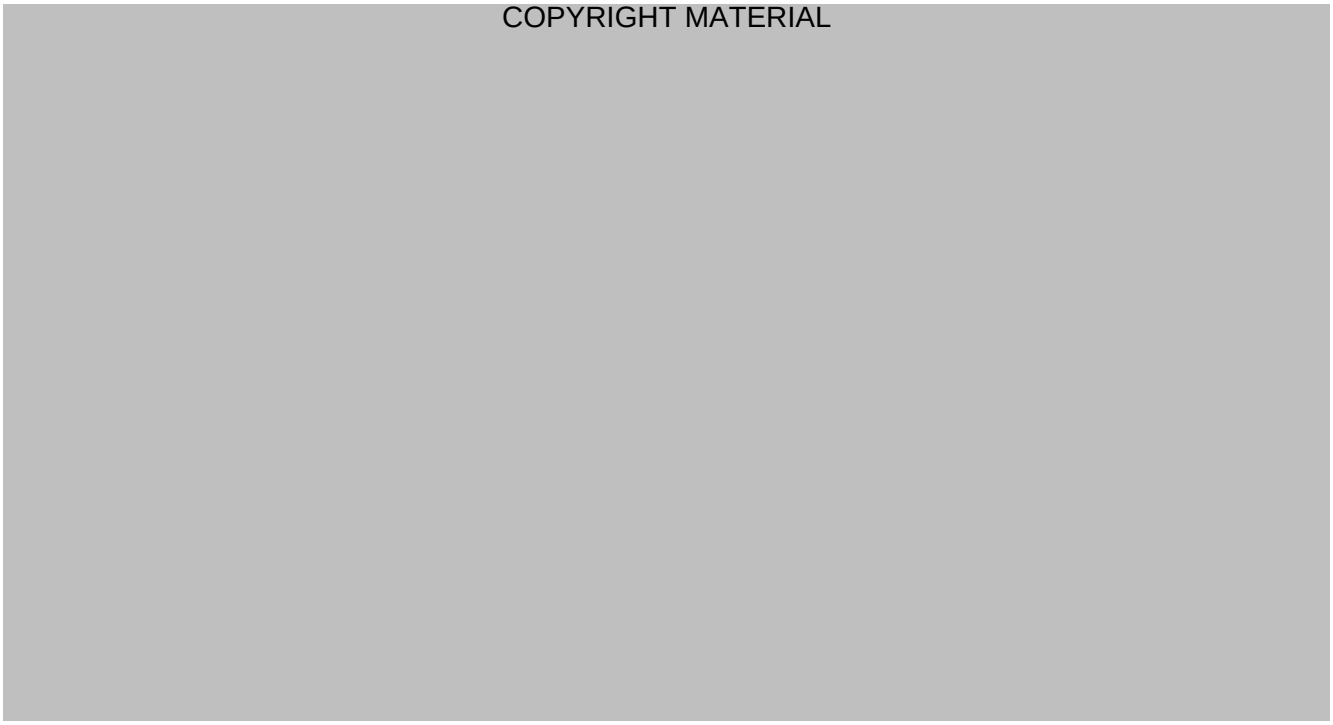
GRA - Global Response Assessment



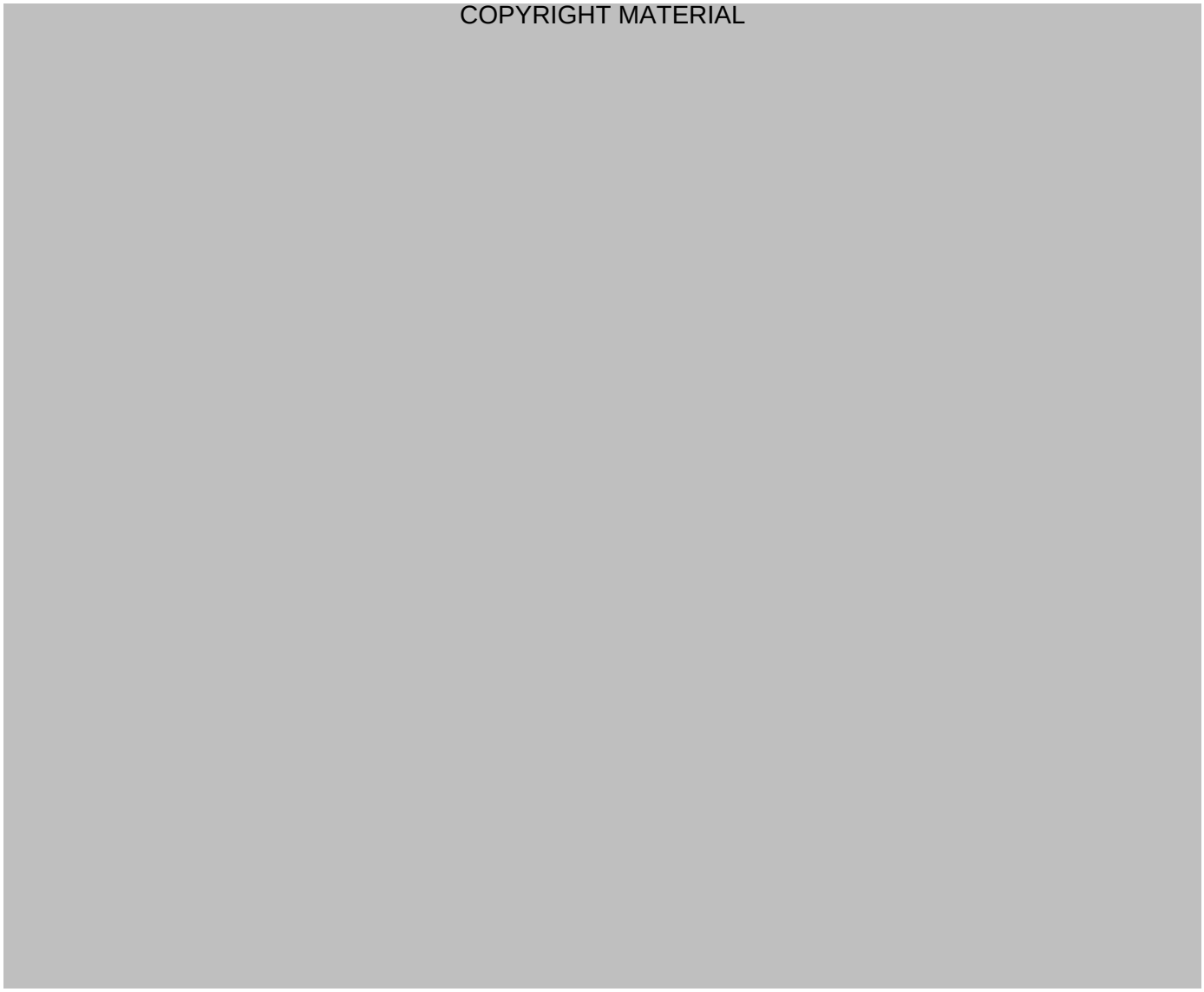
OAB-Q Short Form – Over Active Bladder Questionnaire



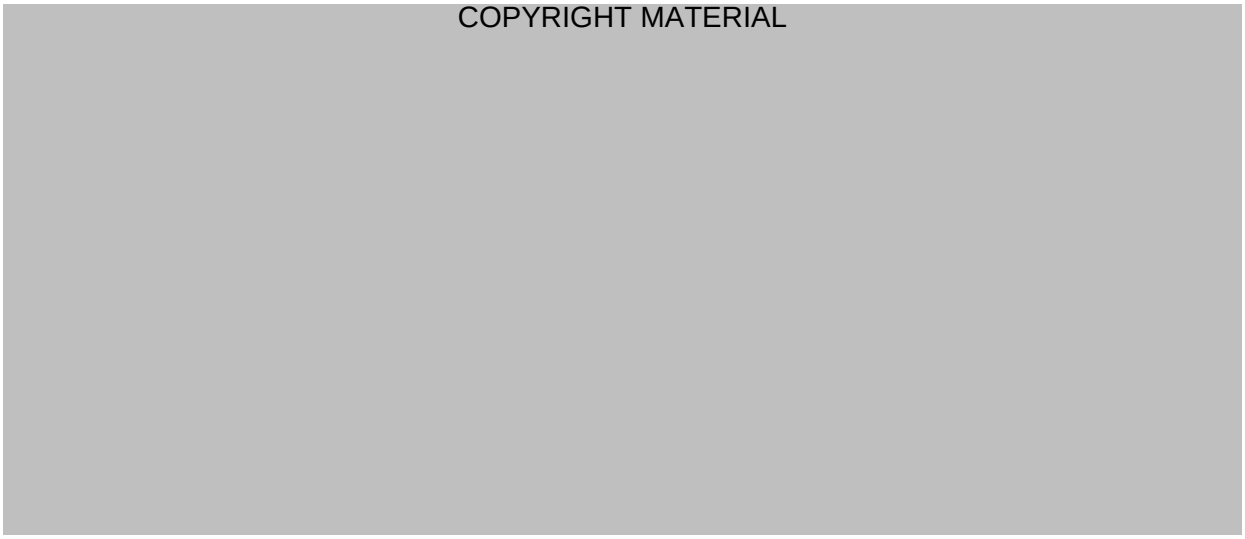
PPBC - Patient Perception of Bladder Condition



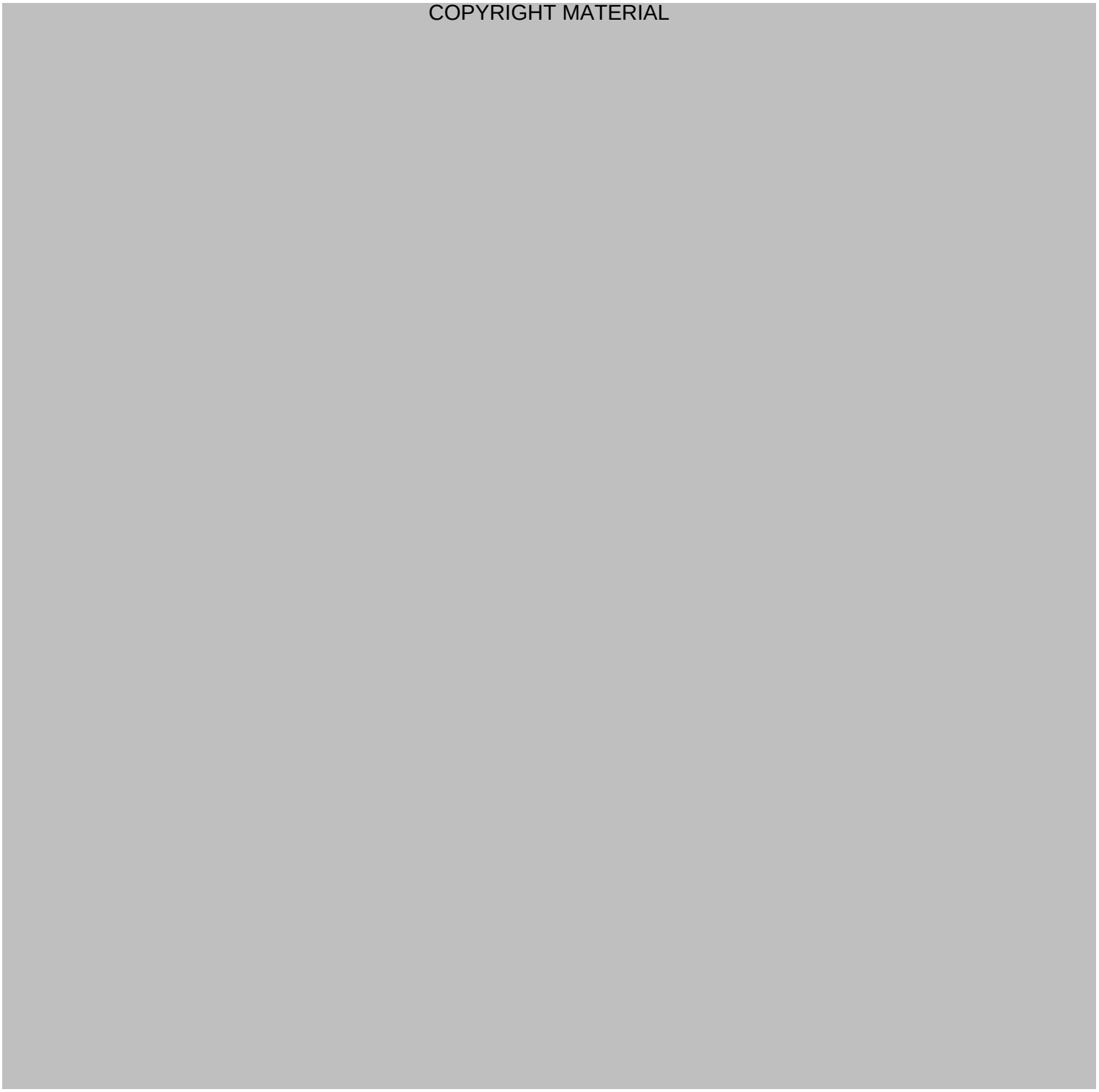
BSWC – Benefit, Satisfaction and Willingness to Continue Questionnaire

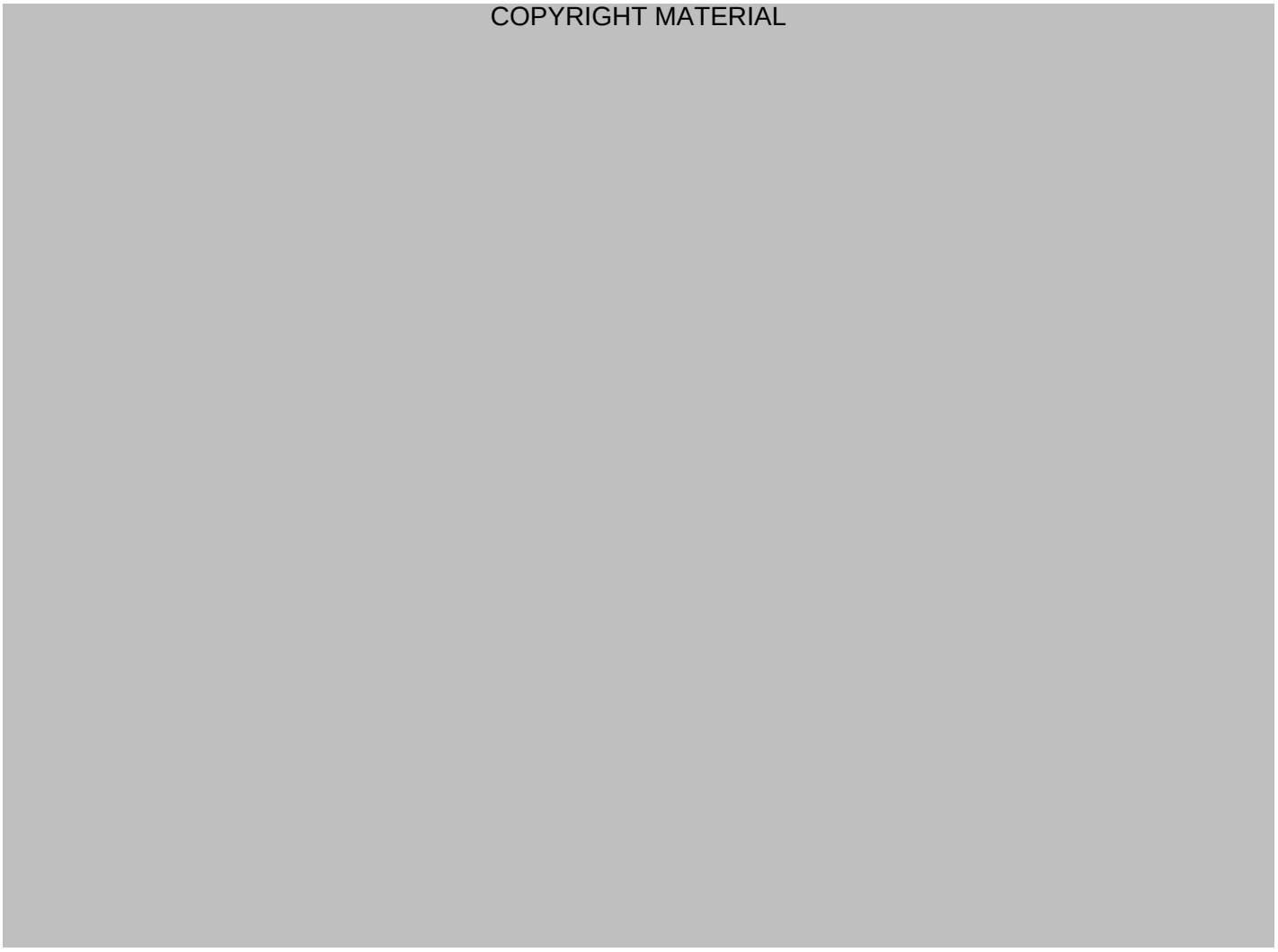


VAS for Treatment Satisfaction – 11 Point Visual Analog Scale for Treatment Satisfaction



PUF – Pelvic Pain and Urgency/Frequency Scale

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O´Leary/Sant VOIDING AND PAIN INDICES

Patient Overall Rating of Improvement in Symptoms Questionnaire