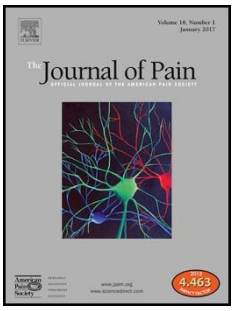
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Research design characteristics of published pharmacologic randomized clinical trials for irritable bowel syndrome and chronic pelvic pain conditions: an ACTTION systemic review.

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Highlights

- Clinical trial design for abdominal and pelvic pain conditions is challenging
- Review of RCT entry criteria and endpoints in representative conditions is provided
- Encouraged future research areas to inform trial design are discussed

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Abstract

Chronic pain conditions occurring in the lower abdomen and pelvis are common, often challenging to manage, and can negatively affect health-related quality of life. Methodological challenges in designing randomized clinical trials (RCTs) for these conditions likely contributes to the limited number of available treatments. The goal of this systematic review of RCTs of pharmacologic treatments for irritable bowel syndrome and 3 common chronic pelvic pain conditions are to (1) summarize the primary endpoints and entry criteria and (2) evaluate the clarity of reporting of important methodological details. In total, 127 RCTs were included in the analysis. The most common inclusion criteria were a minimum pain duration (81%), fulfilling an established diagnostic criteria (61%), and reporting a minimum pain intensity (42%). Primary endpoints were identified for only (57%) of trials. These endpoints, summarized in this article, were highly variable. The results of this systematic review can be used to inform future research to optimize the entry criteria and outcome measures for pain conditions occurring in the lower abdomen and pelvis, to increase transparency in reporting to allow for proper interpretation of RCT results for clinical and policy applications, and to facilitate the aggregation of data in meta-analyses.

Perspective This article summarizes entry criteria and outcome measures and the clarity of reporting of these important design features in RCTs of IBS and 3 common chronic pelvic pain conditions. These results can be used to improve design of future trials of these largely unaddressed pain conditions.

Key words interstitial cystitis / bladder pain syndrome, chronic prostatitis / chronic pelvic pain syndrome, and vulvodynia, RCT reporting

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Introduction

Chronic pain conditions occurring in the lower abdomen and pelvis are prevalent, often challenging to manage, and can negatively affect health-related quality of life, including psychosocial and sexual well-being [3, 8, 25, 27, 32, 37]. Very few U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) approved treatments currently exist for these conditions. The dearth of treatments arises, in part, from methodological challenges in designing randomized clinical trials (RCTs) to evaluate the efficacy of novel treatments in these conditions. First, pain in the lower abdomen often co-occurs with other symptoms (e.g., frequent urination, diarrhea, constipation) that can affect pain severity [24]. Additionally, the condition may involve pain flares (i.e., periods with increased symptom severity) and pain may occur only during specific activities (e.g., sexual activity [27, 29]). These characteristics make it challenging to design a single primary endpoint that is clinically meaningful to patients and responsive to treatment. Although it is possible to assess multiple outcomes in RCTs, in order to adequately evaluate the overall effect of a treatment in conditions with multiple symptoms, identifying a single primary endpoint or statistically adjusting for multiple primary analyses is necessary to minimize false positive conclusions in clinical trials. Unlike in other chronic pain conditions that have typically used the 0 – 10 numeric rating scale of pain intensity for the primary endpoint, RCTs investigating chronic pain conditions occurring in the lower abdomen and pelvis may require more appropriately targeted endpoints (e.g., a summary of pain intensity over multiple weeks to capture fluctuating symptoms or an endpoint that incorporates improvements in pain and another symptom).

A second challenge of conducting RCTs in lower abdominal chronic pain conditions is defining the study entry criteria. In addition to established diagnostic criteria (e.g., [11, 15, 18, 19]), study entry criteria must address how other potential causes of pain in the region (e.g., infection, cancer) will be excluded and whether medications that could affect the symptoms of

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interest will be permitted in the trial. Additionally, IBS and pelvic pain conditions often present concurrently or with other chronic pain conditions [4, 7, 17, 23, 24, 33] which could impede participants' ability to accurately report pain associated with the condition being studied [31]. Decisions regarding these entry criteria could affect the assay sensitivity (i.e., the ability of a RCT to detect a treatment effect if one truly exists), generalizability, and feasibility of the trial.

To our knowledge, with the exception of 1 review published over 15 years ago on IBS trials [2], no systematic reviews have summarized the entry criteria and outcome measures used in RCTs for IBS and chronic pelvic pain conditions. Consequently, the current article presents a systematic review of RCTs of pharmacologic treatments for IBS and 3 common chronic pelvic pain conditions (i.e., chronic prostatitis / chronic pelvic pain syndrome (CP/CPPS), (interstitial cystitis / bladder pain syndrome (IC/BPS), and vulvodynia) [5, 6, 20, 26] that can have a substantial adverse effect health-related quality of life [3, 8, 25, 27]. This systematic review had 3 goals: (1) to summarize the entry criteria in these RCTs, (2) to summarize the primary endpoints in these RCTs, and (3) to evaluate the clarity of reporting of methodological details that are essential for interpretation of the results of RCTs. This summary of entry criteria, endpoints, and reporting clarity can be used to inform future research directed toward optimizing the design of RCTs for IBS and these chronic pelvic pain conditions and identify areas for improvement in publications of future trials to maximize the interpretation of results by clinicians, policy makers, and researchers.

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Methods

Article identification

Articles reporting RCTs investigating treatments for pain associated with irritable bowel syndrome (IBS), chronic prostatitis / chronic pelvic pain syndrome (CP/CPPS), (interstitial cystitis / bladder pain syndrome (IC/BPS), and vulvodynia, or for "chronic pelvic pain" published

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between January 1973 and April 2016 were identified in a PubMed search performed by a medical librarian (see Appendix 1 for search strategy). A second PubMed search was conducted to identify articles that studied treatments that are approved for use by the European Medicines Agency (EMA) or U.S. Food and Drug Administration (FDA) specifically for use in the 4 included conditions. We chose to examine multiple pain conditions that affect the abdominal and lower pelvis areas in a single review because they share common features that pose design challenges for defining entry criteria and outcome measures in clinical trials (i.e., the pain symptoms often co-occur with other symptoms or occur only during specific activities). We chose these conditions because they are common [5, 6, 20, 26], have substantial adverse impacts on health-related quality of life (e.g., sexual dysfunction and psychological distress) [3, 8, 25, 27], are representative of multiple organ systems (i.e., gastrointestinal, urological, gynecological) and include conditions specific for men and women. In order to cover each condition adequately in a single manuscript, we limited the review to 4 representative abdominal pain conditions. We examined only a single treatment class (i.e., pharmacologic) so that we could focus on a limited number of research design considerations and methodologic issues. The search hits were each screened for inclusion by 2 authors (KBI, JYC, or RAK) independently. Included articles (1) reported double-blind, placebo controlled RCTs that evaluated the efficacy of a treatment for 1 of the 4 specific conditions (i.e., IBS, CP/CPPS, IC/BPS, vulvodynia) or “chronic pelvic pain” not otherwise defined and (2) investigated pharmacologic interventions delivered orally, topically, intravenously, bolus injection, or bladder instillation. RCTs for surgical procedures and non-pharmacological treatments such as electrical stimulation, acupuncture, neuromodulation therapies, nutritional supplements and probiotics, psychotherapy, and physical therapy were excluded. Articles that investigated bacterial prostatitis were also excluded. Bacterial prostatitis was excluded from the study because we did not consider it to be a pain condition as it has a known pathological cause (i.e., recurrent infection) and is treated with antibiotics. Finally, articles that were identified by the search based

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on the term “chronic pelvic pain” but that included patients with conditions that were not examined in this review (e.g., endometriosis) were excluded.

Data extraction

A coding manual (Appendix 2) was developed to extract eligibility criteria, primary outcome measures, endpoints, data analyses, and adjustment for multiplicity in these trials. The manual was pre-tested and modified for content by JSG, KBI, and RAK using trials that did not meet the criteria for inclusion. This was performed in 3 rounds (9 trials total). The final list of the 126 identified articles (127 trials) was randomized and each trial was coded independently by 2 authors (from among JYC, JSG, KBI, RAK, SMS). The pre-testing process was terminated after the third round because no differing interpretations by coders or questions regarding the manual’s clarity occurred and no further improvements to the manual were necessary. The data were reviewed and discrepancies due to oversight were adjusted by KBI. Differences in interpretation were adjudicated by KBI in conjunction with JSG. For the purposes of this analysis we used the following definitions (1) *primary outcome measure* - any instrument used to measure the outcome of a trial that the authors identified as primary or that was the sole instrument used to assess efficacy in the trial (e.g., 0 – 10 NRS for pain intensity); (2) *primary endpoint* – how the primary outcome measure(s) was used (e.g., mean pain intensity on a daily 0 – 10 NRS at endpoint; 0 – 10 NRS used to define response in order to identify “treatment responders” who reported a 30% improvement in pain intensity from baseline to endpoint); (3) *primary analysis* – identification of the primary endpoint, the statistical test used to compare groups, and which groups were compared in the analysis considered primary.

Statistical analyses

Descriptive statistics were used to characterize trial design features and clarity of reporting in the total sample by condition (i.e., chronic pelvic pain, CP/CPPS, IBS, IC/BPS, and

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vulvodynia) and by treatment type, that is treatments that have a potential analgesic mechanism (e.g., opioids, antidepressants, antiepileptics, NSAIDs) vs. those that target non-pain symptoms (e.g., constipation, diarrhea). For these analyses, the number of trials was used in the denominator (i.e., 127 for the entire sample).

Results

Coder discrepancies

A total of 4011 survey items were coded; 514 (13%) discrepancies occurred. Of those 511 discrepancies, 408 (80%) were due to oversight and 106 (21%) were due to differences in interpretation.

Trial characteristics

Of the 750 records identified in our first PubMed search, 628 articles were excluded, leaving 122 articles that met the eligibility criteria (Figure 1). Of the 99 publications found in the second set of PubMed searches, 67 articles were excluded, leaving 32 articles that met the eligibility criteria (1 of which reported the results from 2 RCTs that were coded separately). Of the 32 eligible articles from the second search, 28 were already included in the results of the first PubMed search (Supplemental Figure 1), leaving a total of 126 articles that reported 127 RCTs in our final set (See Appendix 3 for list of included articles). The reasons for exclusion are outlined in Figure 1 and Supplemental Figure 1.

The articles were published between 1973 and 2016, with approximately two-thirds published between 2003 and 2016. The majority of trials evaluated treatments for IBS (n=86, 68%). Comparable numbers of trials investigated treatments for IC/BPS (n=19, 15%) and CP/CPPS (n=16, 13%), with the remaining trials including patients with “chronic pelvic pain” with no specific condition criteria (n=4, 3%) and vulvodynia (n=2, 2%). The most frequently examined

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treatments were anti-spasmodic agents (n=37, 29%), anti-constipation agents (n=12, 9%), anti-inflammatory medications (n=9, 7%), tricyclic anti-depressants (n=7, 6%), and botulinum toxin (n=7, 6%). Most experimental treatments were delivered orally (n=110, 87%). All but 6 trials used an inactive placebo in the control group (n=121, 95%). Almost two-thirds of the trials reported at least some industry sponsorship (n=80, 63%) (Table 1).

Eligibility criteria

The most common inclusion criterion was a minimum pain duration (n=103, 81%) (Note: although 49 of these trials did not specify a minimum pain duration in the entry criteria, they based eligibility on the Rome Criteria for IBS that requires a minimum pain duration of 6 months). The next most common inclusion criteria were fulfilling an established diagnostic criteria (e.g., Rome Criteria for IBS [11], Friedrich's criteria for vulvodynia [15], NIDDK IC/BPS criteria [18]; n=78, 61%) and reporting a minimum pain intensity (n=53, 42%). The presence of a comorbid condition associated with the abdominal/pelvic area (e.g. urinary tract infection, kidney stone, anal fissure, recent surgery) was the most common exclusion criterion (n=96, 76%). Eighty of these 96 (83%) trials reported some kind of diagnostic imaging (e.g., colonoscopy endoscopy), physical examination (e.g., pelvic or rectal exam), or laboratory testing (e.g., urinalysis or biopsy) to rule out these other conditions (Table 2). Fifty-four trials (43%) excluded participants who had previously undergone abdominal surgery. Eighty-six trials (68%) prohibited the use of 1 or more concomitant drugs that could affect pain. The most frequently prohibited drugs were opioids (n=37, 43%), antispasmodics/anticholinergics (n=27, 31%), "treatments for the condition" or that could affect efficacy evaluation (without further explanation) (n=21, 24%), antidepressants (n=17, 20%), and anti-inflammatory drugs (n=13, 15%) (Table 2). Common eligibility criteria by individual conditions and treatment type are illustrated in Supplemental Tables 1 and 2.

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Outcome measures and analyses

A single primary outcome measure was identified for seventy-eight (61%) trials. For 11, multiple primary outcome measures (9%) were identified. When considering all of the included trials, some of the most common primary outcome measures were applicable only to IBS trials because over half of the trials reviewed investigated IBS. The 2 types of primary outcome measures that were used most frequently were (1) a composite score including pain and non-pain symptoms, and (2) a single question evaluating disease-specific symptom relief (e.g., "IBS symptom relief"), (n=15, 17% for each). The next most common primary outcome measures were a single question evaluating IBS or abdominal pain and discomfort relief (n=12, 13%) and pain intensity (n=11, 12%). Seventy-two (57%) trials identified a primary endpoint. The primary endpoints used most frequently were: (1) response defined as adequate pain relief for a certain percentage of time (n=9, 13%), (2) response defined as adequate IBS symptom relief for a certain percentage of time (n=9, 13%), (3) severity or change from baseline in pain at endpoint (n=8, 11%), (4) severity or change from baseline in pain and non-pain composite at endpoint (n=7, 10%), and (5) response based on adequate symptom relief at endpoint (n=6, 8%). Pain intensity was more frequently used as the primary outcome measure in trials evaluating treatments from drug classes with known analgesic efficacy as compared to trials using other treatments (e.g., anti-constipation agents) (25% vs. 9%, respectively). Primary outcome measures and primary endpoints by pelvic pain condition and treatment type are presented in Supplemental Tables 3 and 4.

Items from diaries that were used by patients to record symptoms related to the condition (e.g., number of defecations or urinations per day or quality of defecation; n=83, 65%) and pain intensity (n=82, 65%) were the most common non-primary outcome measures reported for the included trials. Other non-primary outcome measures included composite measures that included pain and non-pain symptoms (n=43, 34%) (Table 4).

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At least one primary analysis was identified for 55 trials (43%); 10 of these (18%) identified multiple primary analyses. Eight of these 10 trials (80%) adjusted for multiplicity, with a majority (63%) using a gatekeeping or hierarchical procedure to do so. The other 3 approaches employed were co-primary endpoints that both were required to be statistically significant for the trial to be considered a success (n=1, 13%), the Bonferroni method (n=1, 13%), and a combination of a gatekeeping method and Bonferroni method (n=1, 13%).

Reporting of study design, participation, and comorbid conditions

The length of time that participants were treated with the experimental medication and the duration of follow-up after randomization was reported for all 127 trials. The median duration that participants were treated with experimental medication was 12 weeks (interquartile range [IQR], 4-12). The median number of weeks that participants were followed after randomization was 12 weeks (IQR, 8-16). The number of participants who were screened and randomized, completed the trial, and were included in the analyses is reported in Table 5. Fifty-eight trials (46%) reported the reasons that patients were not enrolled in the trial (e.g., did not meet eligibility criteria, did not complete required questionnaires, refused to participate).

Eight (6%) of the included trials reported the percentage of participants with at least 1 comorbid mental health or pain condition. In these 8 trials, the most frequently reported comorbid conditions were depression (n=5, 63%), anxiety (n=2, 25%), and endometriosis (n=2, 25%). Two of the 8 trials (25%) used a minimum score on a patient self-report or questionnaire or clinician-rated interview (e.g., minimum score on the Hamilton Rating Scale for Depression [21]) to identify a comorbid condition, while 4 of the trials (50%) did not report their method. One trial used a medical chart review and another used patient-identified comorbid conditions (e.g., patient reports that they are depressed or that a doctor previously diagnosed them as being depressed) to identify comorbid conditions.

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Discussion

As would be expected, the results of this systematic review identified variability in eligibility criteria and outcome measures among trials of IBS and 3 common chronic pelvic pain conditions. However, this variability was also observed within trials of the same conditions. Exclusion of co-morbid conditions that could cause related symptoms in the same part of the body and requirement of a minimum pain duration were included as entry criteria in at least three-quarters of the trials. However, fewer than half of the trials required a minimum pain severity at baseline. For many chronic pain conditions, a minimum baseline pain severity is one of the most common inclusion criteria used in RCTs in order to minimize the chance of a "floor effect" (i.e., inability to detect an improvement in mild symptoms) [12]. Interestingly, co-morbid pain conditions outside the abdominal and pelvic area (e.g., fibromyalgia, tension-type headache) were infrequently listed as an exclusion criterion and participants' characteristics in regards to co-morbid pain or mental health conditions were reported for only 6% of trials. Since co-morbid pain and mental health conditions are common and can affect the experience and reporting of pain [1, 31], research examining how inclusion or exclusion of these patients affects the assay sensitivity and generalizability of IBS and pelvic pain trials would be valuable to optimize clinical trial design. However, exclusion of certain conditions may be challenging when there are no well-accepted diagnostic criteria. Additionally, considering the overlap among many pelvic pain conditions exclusion of co-occurring conditions will inhibit recruitment and generalizability. It was also interesting that few trials (9%) prohibited hormone treatments (e.g., corticosteroids and androgens), given that these can affect pain in the lower abdominal and pelvis area [22, 28].

The most common type of primary outcome measure (i.e., a composite outcome measure incorporating pain and non-pain symptoms) was reported in only 17% of trials, although this percentage was higher in trials of IC/BPS and CP/CPPS (i.e., 53% and 64%,

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respectively). The high variability in primary outcome measures in the included trials is not surprising given the complicated nature of the symptom presentation in these conditions. Similarly, we identified a considerable amount of variability in how the outcome measures were incorporated into trial endpoints. For example, in IBS trials, outcome measures were used to define symptom severity at the trial endpoint and also to define “responders” based on varying time frames of response (e.g., response at endpoint vs. over a certain percentage of time throughout the trial). The FDA and EMA guidances both recommend endpoints that identify responders based on improvement in both pain and bowel function over a certain percentage of time throughout the study [13, 36]. Only 8% of IBS trials reported this type of endpoint; however, this is not surprising considering the guidances were published in 2012 and 2014 and only 6% of the IBS trials were published after 2014. Furthermore, the FDA guidance suggests that improvement in pain alone could be considered a primary endpoint in trials of IBS as long as other IBS symptoms are not worsened by the experimental treatment. Within the trials that identified a primary outcome measure, pain intensity was primary in only 25% of the IBS trials that evaluated treatments in drug classes with known analgesic efficacy. Use of a primary outcome measure that evaluates pain alone would be expected to improve assay sensitivity in trials designed to evaluate efficacy of an analgesic that lacks a mechanism that would be expected to improve other symptoms associated with the condition.

Both the FDA and EMA guidances on IBS acknowledge that their recommended outcome measures for IBS have yet to be validated [13, 36]. Regulatory guidances are not available for the other conditions included in this review. Given the regulatory guidance and the high level of variability in the primary endpoints that we identified in this review, it is clear that significant work remains to validate trial endpoints for specific chronic pelvic pain conditions chronic pelvic pain syndrome.

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Regardless of whether a consensus is available on the optimized primary outcome measures, endpoints, and analyses to use for trials in these conditions, it is important that RCT investigators pre-specify a single primary analysis or adjustment for multiplicity in order to decrease the chance of a false positive conclusion [16, 34]. A primary analysis or adjustment for multiplicity in the primary analysis was identified for only approximately 40% of the trials reviewed. This result identifies a major area for improvement in the design and reporting of IBS and pelvic pain trials. The included trials utilized several strategies to address multiplicity, either by incorporating multiple symptoms into a single primary endpoint or using statistical strategies. These strategies included (1) a responder analysis that required a predetermined degree of improvement in multiple symptoms, (2) a composite outcome measure that incorporates assessment of multiple symptoms in a single composite score, (3) a hierarchical gatekeeping approach that pre-specifies the order of analysis of individual outcome measures in which the treatment effect of each subsequent symptom is only tested if the previous analysis yields a statistically significant result [9, 10], and (4) a Bonferroni correction, which involves adjusting the significance level of each analysis so that the overall false positive rate is protected, typically to 5% [30, 35]. All of these methods to evaluate multiple symptoms without inflating the false positive rate in a RCT provide information regarding the magnitude of change in each of the symptoms with the exception of the composite score. Changes in a composite score can be driven by a single symptom, and therefore it can be difficult to interpret the meaning of a change in composite score. If a composite score is used, sensitivity analyses that investigate the treatment effects on the individual components of the composite are recommended. This fact should be taken into consideration when designing new endpoints for IBS and chronic pelvic pain trials in order to maximize the interpretability of the potential clinical impact of treatments identified in RCTs.

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Several limitations of this review should be acknowledged. First, we only evaluated published articles reporting on RCTs in IBS, CP/CPPS, IC/BPS, vulvodynia and “chronic pelvic pain” and not those that specifically recruited patients with other chronic or acute abdominal and pelvic pain conditions (e.g., endometriosis; dysmenorrhea). Second, although important methodological details of RCTs should be reported in publications, it is possible that investigators did not report all eligibility criteria and primary outcome measures used in the trials and that our results may reflect, at least in part, inadequacies in reporting rather than deficiencies in clinical trial design.

In conclusion, our review identified a lack of consensus in the literature on key design features of clinical trials for IBS, CP/CPPS, IC/BPS, vulvodynia, and chronic pelvic pain. Research is necessary to identify research design features and methods that can maximize assay sensitivity and clinical meaningfulness of endpoints in these trials (e.g., secondary analyses that compare the effect sizes associated with different endpoints in existing trial data; qualitative interviews with patients regarding the impact of different symptom patterns). Furthermore, more consistent reporting of design characteristics that are critical to the interpretation of the trial results and for meta-analyses of results across studies is important to improve the dissemination and incorporation of results into clinical practice and management guidelines.

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References

1. Adams LM, Turk DC. Psychosocial factors and central sensitivity syndromes. Curr Rheumatol Rev 11:96-108, 2015.
2. Akehurst R, Kaltenthaler E. Treatment of irritable bowel syndrome: a review of randomised controlled trials. Gut 48:272-82, 2001.
3. Bengtson MB, Aamodt G, Vatn MH, Harris JR. Co-occurrence of IBS and symptoms of anxiety or depression, among Norwegian twins, is influenced by both heredity and intrauterine growth. BMC Gastroenterol 15:9, 2015.
4. Bogart LM, Berry SH, Clemens JQ. Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. J Urol 177:450-6, 2007.
5. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol 6:71-80, 2014.
6. Clemens JQ, Meenan RT, Rosetti MC, Gao SY, Calhoun EA. Prevalence and incidence of interstitial cystitis in a managed care population. J Urol 173:98-102; discussion 102, 2005.
7. Costantini R, Affaitati G, Wesselmann U, Czakanski P, Giamberardino MA. Visceral pain as a triggering factor for fibromyalgia symptoms in comorbid patients. Pain epub ahead of print, 2017.
8. Dalpiaz O, Kerschbaumer A, Mitterberger M, Pinggera G, Bartsch G, Strasser H. Chronic pelvic pain in women: still a challenge. BJU Int 102:1061-5, 2008.
9. Dmitrienko A, Tamhane AC. Gatekeeping procedures with clinical trial applications. Pharm Stat 6:171-80, 2007.
10. Dmitrienko A, Wiens BL, Tamhane AC, Wang X. Tree-structured gatekeeping tests in clinical trials with hierarchically ordered multiple objectives. Stat Med 26:2465-78, 2007.

ACCEPTED MANUSCRIPT

11. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology 150:1257-61, 2016.

12. Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, Chappell A, Chartier K, Cleeland CS, Costello A, Cowan P, Dimitrova R, Ellenberg S, Farrar JT, French JA, Gilron I, Hertz S, Jadad AR, Jay GW, Kalliomaki J, Katz NP, Kerns RD, Manning DC, Mcdermott MP, Mcgrath PJ, Narayana A, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Reeve BB, Rhodes T, Sampaio C, Simpson DM, Stauffer JW, Stucki G, Tobias J, White RE, Witter J. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain 149:177-93, 2010.

13. European Medicines agency. Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome. 2015 [Accessed 08/24/2017] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500173457.pdf.

14. Foster DC, Kotok MB, Huang LS, Watts A, Oakes D, Howard FM, Stodgell CJ, Dworkin RH. The tampon test for vulvodynia treatment outcomes research: reliability, construct validity, and responsiveness. Obstet Gynecol 113:825-32, 2009.

15. Friedrich EG, Jr. Vulvar vestibulitis syndrome. J Reprod Med 32:110-4, 1987.

16. Gewandter JS, Smith SM, Mckeown A, Burke LB, Hertz SH, Hunsinger M, Katz NP, Lin AH, Mcdermott MP, Rappaport BA, Williams MR, Turk DC, Dworkin RH. Reporting of primary analyses and multiplicity adjustment in recent analgesic clinical trials: ACTTION systematic review and recommendations. Pain 155:461-6, 2014.

17. Giamberardino MA, Costantini R, Affaitati G, Fabrizio A, Lapenna D, Tafuri E, Mezzetti A. Viscero-visceral hyperalgesia: characterization in different clinical models. Pain 151:307-22, 2010.

Accepted Manuscript

ACCEPTED MANUSCRIPT

18. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol 140:203-6, 1988.

19. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, Forrest JB, Gordon B, Gray M, Mayer RD, Newman D, Nyberg L, Jr., Payne CK, Wesselmann U, Faraday MM, Interstitial Cystitis Guidelines Panel of the American Urological Association E, Research I. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 185:2162-70, 2011.

20. Harlow BL, Kunitz CG, Nguyen RH, Rydell SA, Turner RM, Maclehose RF. Prevalence of symptoms consistent with a diagnosis of vulvodynia: population-based estimates from 2 geographic regions. Am J Obstet Gynecol 210:40 e1-8, 2014.

21. Hedlung, Vieweg. The Hamilton Rating Scale for Depression. Journal of Operational Psychiatry 10:149-165, 1979.

22. Jarrell JF, Vilos GA, Allaire C, Burgess S, Fortin C, Gerwin R, Lapensee L, Lea RH, Leyland NA, Martyn P, Shenassa H, Taenzer P, Abu-Rafea B, Chronic Pelvic Pain Working G, Sogc. Consensus guidelines for the management of chronic pelvic pain. J Obstet Gynaecol Can 27:781-826, 2005.

23. Lai HH, Jemielita T, Sutcliffe S, Bradley CS, Naliboff B, Williams DA, Gereau RWT, Kreder K, Clemens JQ, Rodriguez LV, Krieger JN, Farrar JT, Robinson N, Landis JR, Network MR. Characterization of Whole Body Pain in Urological Chronic Pelvic Pain Syndrome at Baseline: A MAPP Research Network Study. J Urol 198:622-31, 2017.

24. Lai HH, Krieger JN, Pontari MA, Buchwald D, Hou X, Landis JR, Network MR. Painful Bladder Filling and Painful Urgency are Distinct Characteristics in Men and Women with Urological Chronic Pelvic Pain Syndromes: A MAPP Research Network Study. J Urol 194:1634-41, 2015.

ACCEPTED MANUSCRIPT

25. Naliboff BD, Stephens AJ, Afari N, Lai H, Krieger JN, Hong B, Lutgendorf S, Strachan E, Williams D, Network MR. Widespread Psychosocial Difficulties in Men and Women With Urologic Chronic Pelvic Pain Syndromes: Case-control Findings From the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network. Urology 85:1319-27, 2015.

26. Nickel JC, Downey J, Hunter D, Clark J. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. J Urol 165:842-5, 2001.

27. Petersen CD, Lundvall L, Kristensen E, Giraldi A. Vulvodynia. Definition, diagnosis and treatment. Acta Obstet Gynecol Scand 87:893-901, 2008.

28. Priya K, Rajaram S, Goel N. Comparison of combined hormonal vaginal ring and low dose combined oral hormonal pill for the treatment of idiopathic chronic pelvic pain: a randomised trial. Eur J Obstet Gynecol Reprod Biol 207:141-146, 2016.

29. Pukall CF, Bergeron S, Brown C, Bachmann G, Wesselmann U, Vulvodynia Collaborative Research G. Recommendations for Self-Report Outcome Measures in Vulvodynia Clinical Trials. Clin J Pain 33:756-765, 2017.

30. Sankoh AJ, Huque MF, Dubey SD. Some comments on frequently used multiple endpoint adjustment methods in clinical trials. Stat Med 16:2529-42, 1997.

31. Smith SM, Amtmann D, Askew RL, Gewandter JS, Hunsinger M, Jensen MP, Mcdermott MP, Patel KV, Williams M, Bacci ED, Burke LB, Chambers CT, Cooper SA, Cowan P, Desjardins P, Etropolski M, Farrar JT, Gilron I, Huang IZ, Katz M, Kerns RD, Kopecky EA, Rappaport BA, Resnick M, Strand V, Vanhove GF, Veasley C, Versavel M, Wasan AD, Turk DC, Dworkin RH. Pain intensity rating training: results from an exploratory study of the ACTTION PROTECCT system. Pain 157:1056-64, 2016.

32. Sperber AD, Dumitrascu D, Fukudo S, Gerson C, Ghoshal UC, Gwee KA, Hungin APS, Kang JY, Minhu C, Schmulson M, Bolotin A, Friger M, Freud T, Whitehead W. The

ACCEPTED MANUSCRIPT

global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut 66:1075-1082, 2017.

33. Tu FF, Epstein AE, Pozolo KE, Sexton DL, Melnyk AI, Hellman KM. A noninvasive bladder sensory test supports a role for dysmenorrhea increasing bladder noxious mechanosensitivity. Clin J Pain 29:883-90, 2013.

34. Turk DC, Dworkin RH, Mcdermott MP, Bellamy N, Burke LB, Chandler JM, Cleeland CS, Cowan P, Dimitrova R, Farrar JT, Hertz S, Heyse JF, Iyengar S, Jadad AR, Jay GW, Jermano JA, Katz NP, Manning DC, Martin S, Max MB, Mcgrath P, Mcquay HJ, Quessy S, Rappaport BA, Revicki DA, Rothman M, Stauffer JW, Svensson O, White RE, Witter J. Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. Pain 139:485-93, 2008.

35. U.S. Health and Human Services, Food and Drug Administration. Multiple Endpoints in Clinical Trials: Guidance for Industry. 2017 [Accessed 8/24/2017] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf.

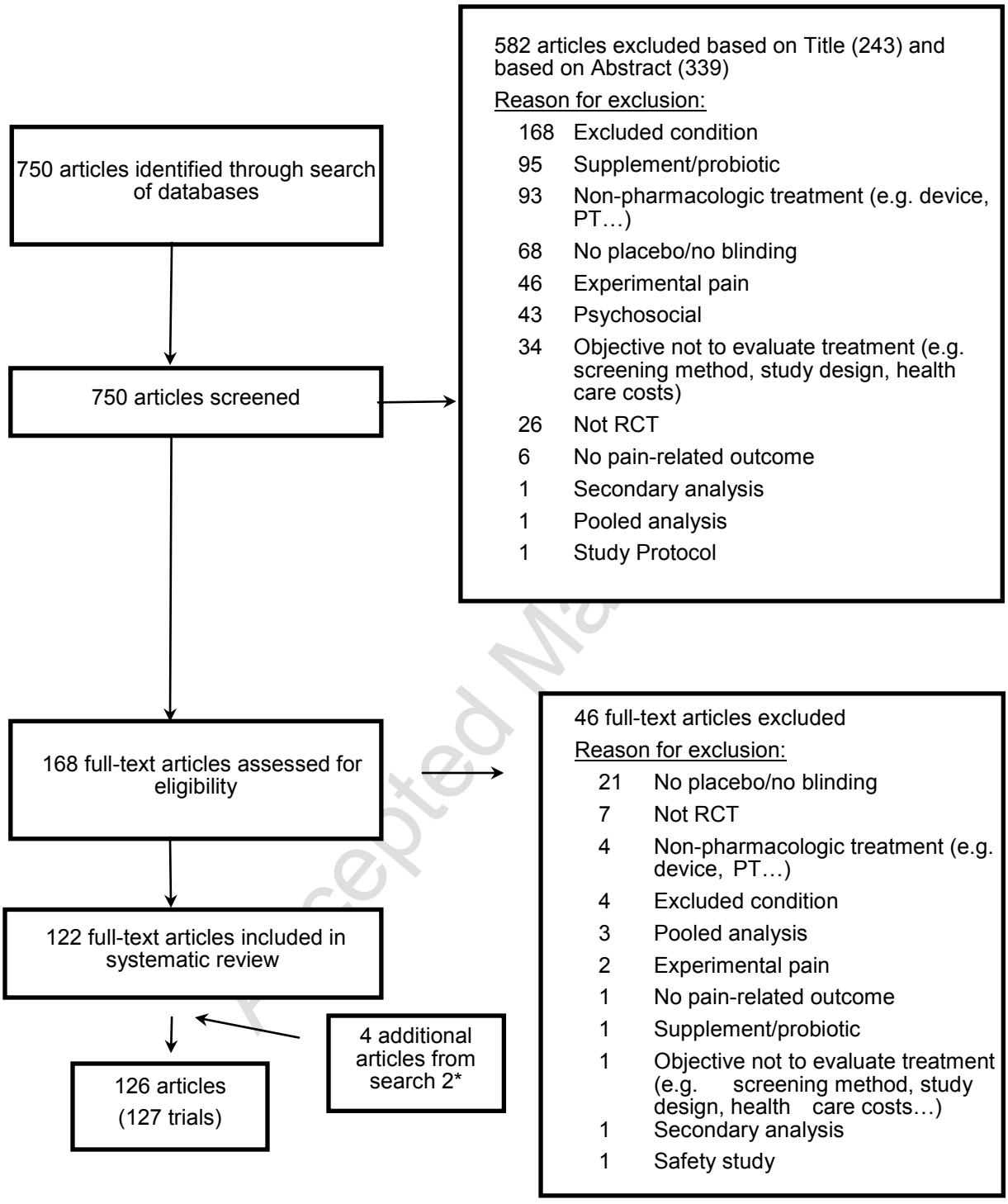
36. U.S. Health and Human Services, Food and Drug Administration. Guidance for Industry: Irritable bowel syntrome -- Clinical evaluation of drugs for treatment. 2012 [Accessed 8/24/2017] https://www.fda.gov/downloads/Drugs/Guidances/UCM205269.pdf

37. Yoon SL, Grundmann O, Koepp L, Farrell L. Management of irritable bowel syndrome (IBS) in adults: conventional and complementary/alternative approaches. Altern Med Rev 16:134-51, 2011.

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Figure 1. PRISMA diagram



* One article reports 2 trials separately and was coded twice (once for each trial)

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Table 1. Trial Characteristics

Characteristic	Frequency (%) or Median (IQR)
Year	
1973-2000	31 (24)
2001-2016	96 (76)
Condition	
Irritable bowel syndrome	86 (68)
Interstitial cystitis / bladder pain syndrome	19 (15)
Chronic prostatitis / chronic pelvic pain syndrome	16 (13)
"Chronic pelvic pain"	4 (3)
Vulvodynia	2 (2)
Treatment	
Anti-spasmodic/anti-diarrheal agent	37 (29)
Anti-constipation agent	12 (9)
Anti-inflammatory	9 (7)
Botulinum toxin	7 (6)
Tricyclic antidepressant	7 (6)
SSRI/SNRI	6 (5)
Antibiotic	6 (5)
Pentosan polysulfate	6 (5)
Urinary retention agent	6 (5)
Opioid	5 (4)
Anticonvulsant	4 (3)
Anti-constipation and possible pain mechanism	4 (3)
Immunotherapy	4 (3)
Anesthetic	2 (2)
Other	12 (9)
Administration route	
Oral	110 (87)
Other injection (e.g., intrathecal, subcutaneous)	10 (8)
Intravesical instillation	3 (2)
IV	2 (2)
Other	2 (2)
Type of control group	
Inactive placebo	121 (95)
Active comparator	4 (3)
Two doses of the same treatment compared	2 (2)
Sponsor*	
Industry	80 (63)
Industry only provided treatment	12 (9)
Government	6 (5)
Academic institution	3 (2)
Foundation	1 (1)
Not reported	25 (20)

Abbreviations: Interquartile range (IQR); Selective serotonin reuptake inhibitor (SSRI); Serotonin and norepinephrine reuptake inhibitors (SNRI)

*"Industry" includes studies that had any support from a pharmaceutical company other than providing drug (regardless of funds from other sources); "Industry only provided treatment" includes studies that were provided drug from a company, but no funds to support the research from that company (regardless of funds from other sources); "Government", "Academic institution", and "Foundation" includes studies that only reported funding from those types of sources.

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Table 2. Reporting of inclusion/exclusion criteria

Criteria	Frequency (%)
Inclusion*	
Minimum duration of pain	103 (81)
Established diagnostic criteria (e.g., Rome criteria for IBS)	78 (61)
Minimum pain intensity	53 (42)
Minimum score on a disease-specific composite measure (e.g. NIH-Chronic Prostatitis Symptom Index)	23 (18)
Diagnosis of disease by clinician (e.g. urologist) that is not based on diagnostic criteria	21 (17)
Physiologic imaging, examination or laboratory testing to confirm diagnosis	13 (10)
Minimum score on a stool consistency score (indicating diarrhea)	10 (8)
Specific location of pain (e.g., lower quadrant abdominal pain)**	9 (7)
Presence of various constipation symptoms***	9 (7)
Presence of urinary symptoms	8 (6)
Refractory to previous treatment****	8 (6)
Presence of abnormal bowel symptoms (not specific to diarrhea or constipation)	5 (4)
Exclusion*	
Comorbid conditions associated with abdominal/pelvic area that could cause pain (e.g. UTI, kidney stone, anal fissure, recent surgery)	96 (76)
Physiologic imaging, examination or laboratory testing to rule out other conditions associated with the abdominal / pelvic area	80 (63)
Imaging (e.g., colonoscopy, endoscopy, barium enema)	59 (46)
Stool culture/parasite test/urinalysis/semen culture	32 (25)
Test for food sensitivities	9 (7)
Fecal occult blood test or urine cytology	8 (6)
Mucosal/colonic/duodenal biopsy	6 (5)
Physical exam	6 (5)
PSA level/expressed prostatic secretions	7 (6)
Pelvic/rectal exam	4 (3)
Four-glass test	3 (2)
Abdominal surgery procedures	54 (43)
Current or previous history of alcohol or drug abuse	43 (34)
Psychiatric conditions (e.g., depression, anxiety)	42 (33)
Malignancy	39 (31)
Comorbid pain conditions not associated with abdominal/pelvic area	10 (8)
Use of alcohol/drugs/cigarettes over a certain amount	6 (5)
Max pain intensity	3 (2)
Max pain duration	1 (1)
Prohibited use of certain drugs	86 (68)
Opioids (includes trials that stated drugs that affect gut motility were excluded)	37 (43)
Antispasmodics/anticholinergics	27 (31)
Treatments “for the condition” with no further clarification or “could affect evaluation of efficacy”	21 (24)
Antidepressants	17 (20)
Anti-inflammatory drugs	13 (15)
All analgesic medications	9 (10)
Hormones/steroids	8 (9)
Anticonvulsants	4 (5)

Abbreviations: Irritable bowel syndrome (IBS), National Institutes of Health (NIH) Urinary tract infection (UTI)

*Inclusion and exclusion criteria include most common criteria, and criteria pre-specified in our review protocol (e.g., max pain intensity and max pain duration)

**Does not include a general statement of “abdominal pain”

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***Some combination of maximum number of spontaneous bowel movements, stool straining, hard stools, or sensation of incomplete evacuation
****Previous treatments include antibiotics, non-pharmacological therapy, hydrostatic distension, and intravesical instillations
Note: the denominator for the percentages for each excluded drug is the number of studies that listed any drug exclusion

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Table 3. Reporting of outcome measures and endpoints

Outcome Measure	Frequency (%)
Primary outcome measure (out of 89 that identified a primary outcome measure)	
Composite score including pain and non-pain symptoms	15 (17)
Disease-specific symptom relief (e.g., "IBS symptom relief")	15 (17)
IBS or abdominal pain and discomfort relief	12 (13)
Pain intensity	11 (12)
Listed multiple primary outcome measures, one of which was pain intensity	7 (8)
"Symptom relief" (not disease-specific)	4 (4)
Listed multiple primary outcome measures, one of which was NOT pain intensity	4 (4)
Pain intensity/discomfort	3 (3)
Stool consistency	3 (3)
Pain relief	2 (2)
Composite of pain intensity and frequency	2 (2)
Number of days with pain	2 (2)
Biomarker (e.g., number of colonic immune cells, enterochromaffin cells)	2 (2)
Other*	7 (8)
Primary endpoint (out of 72 that identified a primary endpoint)**	
Response defined as adequate pain relief for a certain percentage of time	9 (13)
Response defined as adequate IBS symptom relief for a certain percentage of time	9 (13)
Severity or change from baseline in pain at endpoint	8 (11)
Severity or change from baseline in pain and non-pain composite at endpoint	7 (10)
Response based on adequate symptom relief at endpoint	6 (8)
Responders defined as having both pain relief and improved bowel movements for a specific percentage of time	4 (6)
Model that incorporates relief or improvement over the duration of the study (e.g., RM-ANOVA)	3 (4)
Response based on improvement in stool consistency score at endpoint or for a certain percentage of time	3 (4)
Biomarker at endpoint or change from baseline	2 (3)
Stool consistency or constipation at endpoint	2 (3)
Summary of change in pain intensity at a specified time after receiving a dose of medication	2 (3)
Response defined as percentage change in pain and non-pain composite at endpoint	2 (3)
Response based on change from baseline in pain and non-pain composite	2 (3)
Response based on improvement in pain severity and frequency at endpoint	1 (1)
Other	11 (15)

Abbreviations: Irritable bowel syndrome (IBS) Repeated Measures – Analysis of Variance (RM-ANOVA)
*Examples include a disease-specific quality of life measure and the "tampon test" which evaluates pain intensity upon insertion of a standardized tampon [14].
**Includes 4 endpoints from 2 trials that identified two primary endpoints.

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Table 4. Reporting of non-primary outcome measures

Non-primary, pain or pain-related measures (out of 127)	
Diary (included number of defections per day or number of urinations per day or nocturia or quality of defecation)	83 (65)
Pain intensity	82 (65)
Composite score including pain + non-pain symptoms	43 (34)
QoL measure specific to disease	30 (24)
Depression measure	23 (18)
Anxiety measure	20 (16)
QoL measure (not disease specific)	16 (13)
Sleep quality measure	4 (3)
Pain intensity during a specific activity (e.g., urination, sex)	4 (3)
Pain interference with function	3 (2)
Composite score including pain + physical function	1 (1)

Abbreviation: Quality of life (QoL)

Table 5. Reporting of study participation

Study Period	Number (%) of trials or Median [IQR] of participants
Specified the number of participants who were screened Number screened	65 (51) 349 [137 – 1238]
Specified the number of participants who were randomized Number randomized	125 (98) 102 [49 – 370]
Specified the number of participants who completed the trial Percent completed	112 (88) 76 [39 – 233]
Specified the number of participants who were included in the analyses Percent included in analyses	68 (54) 94 [42 – 272]
Reported reasons for non-enrollment	58 (46)

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