Evidence-Based Medicine

Development of an Interventional Pain Management Specific Instrument for Methodologic Quality Assessment of Nonrandomized Studies of Interventional Techniques

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Background: The major component of a systematic review is assessment of the methodologic quality and bias of randomized and nonrandomized trials. While there are multiple instruments available to assess the methodologic quality and bias for randomized controlled trials (RCTs), there is a lack of extensively utilized instruments for observational studies, specifically for interventional pain management (IPM) techniques. Even Cochrane review criteria for randomized trials is considered not to be a "gold standard," but merely an indication of the current state of the art review methodology. Recently a specific instrument to assess the methodologic quality of randomized trials has been developed for interventional techniques.

Objectives: Our objective was to develop an IPM specific instrument to assess the methodological quality of nonrandomized trials or observational studies of interventional techniques.

Methods: The item generation for the instrument was based on a definition of quality, to the extent to which the design and conduct of the trial were congruent with the objectives of the study. Applicability was defined as the extent to which procedures produced by the study could be applied using contemporary IPM techniques. Multiple items based on Cochrane review criteria and Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR) were utilized.

Results: A total of 16 items were developed which formed the IPM-QRBNR tool.

The assessment was performed in multiple stages. The final assessment was 4 nonrandomized studies. The inter-rater agreement was moderate to good for IPM-QRBNR criteria.

Limitations: Limited validity or accuracy assessment of the instrument and the large number of items to be scored were limitations.

Conclusion: We have developed a new comprehensive instrument to assess the methodological quality of nonrandomized studies of interventional techniques. This instrument provides extensive information specific to interventional techniques is useful in assessing the methodological quality and bias of observational studies of interventional techniques.

Key words: Methodological quality assessment, evidence-based medicine, comparative effectiveness research, Cochrane Reviews, interventional techniques, risk of bias assessment, nonrandomized trials, observational studies

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Evidence-based medicine, comparative effectiveness research, and guideline development are major focuses in modern medicine of health care research, practice, and policy in improving the organization, delivery, and outcomes of care (1-4). Even though evidence synthesis and development of guidelines through systematic reviews is focused on randomized controlled trials (RCTs), it is understood that this process continues to be dynamic, ever changing, and constantly growing, leading the Institute of Medicine (IOM) to re-engineer its definition of clinical guidelines and systematic reviews in 2011 (3,4). Clinical practice guidelines have been redefined by IOM as statements to include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options (3). In addition to this, systematic reviews have been described as tools to identify, select, assess, and synthesize the findings of similar but separate studies and to help clarify what is known and not known about the potential benefits and harms of drugs, devices, and other health care services (4). IOM also has additionally proposed 8 standards for the development of guidelines (3,4).

At the center of an improvement in patient care is a medical humanism, that seeks to understand the patient as a person, focusing on individual values, goals, and preferences with respect to clinical decisions (5). Modern medicine's present focus on evidence-based practice, whether applied accurately or not, aims to put medicine on a firm scientific footing: experts evaluate the best available data and develop clinical guidelines designed to standardize procedures and therapies (5). The Affordable Care Act, sought a combination of universal coverage and cost containment, as well as the improvement of quality of care. This has proven to be unattainable, as these 2 polarizing issues of humanism and evidence-based practice continue to collide rather than collate (6-11). In the context of evidence-based medicine, clinical decisions are based on the best available scientific data rather than on customary practices or the personal beliefs of health care providers. Thus, in evidence-based medicine, and most recently comparative effectiveness research, the RCT is usually considered of greater evidentiary value for assessing the efficacy of interventions. In addition, the preference for this design is sufficiently strong that when empirical evidence from RCTs is available, "weak" designs are often considered to be of little or no evidentiary value. The manuscripts of vertebroplasty for painful osteoporotic vertebral fractures (12,13), accompanied by an editorial (14) raised multiple questions with regards to the ability of randomized trials to effectively determine the efficacy of an intervention. The editorial by Weinstein (14), described the evidence in the context of comparative effectiveness research as proposed at the time in the American Recovery and Reinvestment Act (7,15,16). Weinstein (14) described that although clinical trials are an integral part of comparative effectiveness research, from a safety and effectiveness standpoint, data from clinical trials combined with those from registries or other large longitudinal databases are necessary to provide the best evidence.

As the evidence continues to emerge, so does the proliferation of RCTs in surgery and interventional pain management (IPM) (2,17-26). The role and place for nonrandomized or observational studies continues to be debated (5,27-30). In fact, Marin et al (31) elaborated on the Cochrane Back Review Group's future and expanded role in assessing nonrandomized studies and diagnostic accuracy studies. Even though randomized trials are at the top of the hierarchy, they are subject to abundant criticism (1,2,5,14,20,21,26-30,32-56). As described earlier, even though the 2 vertebroplasty trials (12,13) provided the best available scientific evidence which was negative, later studies have provided additional evidence illustrating the efficacy and cost effectiveness of vertebroplasty (57-77). Kyphoplasty, which garnered results similar to those of vertebroplasty has not received such negative publicity due to a lack of RCTs (78-83). In fact, both techniques of vertebral augmentation have yielded similar results in independent as well as comparative assessments (58,60-63,65,74,75,78-83). Historically, such results have shown to have no effect on practice patterns with coronary artery revascularization (84-94). However, the prevalence of bypass surgery has decreased in favor of advanced percutaneous technology with stents. Despite some negative studies, facet joint interventions (32,56,95-100), lumbar interlaminar and caudal epidurals (17,21,26,33-36,56,95-99,101-103), and various other treatments including multiple interventional techniques and surgical interventions (56,95-123) continue to increase. In contrast to this general growth trend in the face of the publication of negative trials, the utilization of vertebroplasty and kyphoplasty seem to have flattened (124,125). In fact, in a referral pattern analysis at 2 academic medical centers (125), the 2 trials (12,13) changed referring physicians' understanding of the role of vertebroplasty and diminished their willingness to refer osteoporotic

compression fracture patients. Consequently, negative trials, whether randomized or observational, may have differing effects. A review of the analysis of utilization patterns and negative evidence or even positive evidence illustrates the role of appropriate conduct of various types of trials which should be conclusive and may include non-randomized studies.

In many situations, randomized controlled designs are not feasible, with the only available data from nonrandomized or observational studies (2,5,28-31,126-128). Consequently, it is in some cases essential to utilize evidence derived from observational or nonrandomized studies. The literature is rampant with descriptions showing that coherent and transparent decision rules are needed for deciding when only to include RCTs, when to include non-RCTs, and when to include other types of evidence (127). The importance of observational studies becomes more prominent when RCTs are not available or are inconclusive. The addition of information from observational studies, systematic reviews, and meta-analysis may aid in clinical reasoning and establish a more solid foundation for causal inferences. Shrier et al (128) found that the advantages of including both observational studies and RCTs in a metaanalysis could outweigh the disadvantages in many situations and that observational studies should not be excluded a priori. Furthermore , Shrier (129) in a systematic review which included RCTs and observational studies, reached the conclusion that stretching immediately before exercise would not reduce injury, This conclusion was contrary to the opinion prior to 1999 that stretching immediately before exercise was a benefit, a recommendation derived from 4 small RCTs. Shrier's conclusion (129) is still considered to be valid despite numerous trials, investigations, and systematic reviews opining that further evidence is needed to arrive at a definitive conclusion, even after 15 years of research (130-137). While it is generally assumed that RCTs can contradict the findings of highly publicized observational studies and that RCTs provide the last word, some observational studies may contradict the findings of highly publicized RCTs. Ioannidis (138) assessed the contradictory and initially stronger effects in 9 of 49 highly cited randomized trials. Of these, 16% were contradicted by subsequent studies, 16% found effects that were stronger than those of subsequent studies, 44% were replicated, and 24% remained largely unchallenged. Tatsioni et al with Ioannidis as co-author (139) also concluded that claims from highly cited observational studies persist and continue to be supported in the medical literature despite strong contradictory evidence from randomized trials. They (139) assessed 2 highly cited epidemiological studies that proposed major cardiovascular benefits associated with vitamin E in 1993 and showed that even in 2005, 50% of citing articles remained favorable. Similarly, favorable citations to beta-carotene, long after evidence contradicted its effectiveness, did not consider the contradicting evidence. Yakoot (140), in comparison of observational studies and RCTs in use of vitamin E and omega-3 concluded that in this era of an overabundance of data, it should be emphasized in articles that are short and quick to read that it is important to consider not only the level of evidence "as dictated by the study design and sample size" but also the relevance of the evidence. Yakoot (140) described that the studies tell us about populations while we treat individuals. The type of the studied individuals, the enrollment criteria, the methodology, the dose of the studied drug, and the combined medication in the study should be clearly considered whenever the reported results are to be generalized beyond the specific situation studied. He felt that the encouragement and acceptance of more publications of high quality, real-world pragmatic clinical studies, case series, and real physician experience, in addition to the already prioritized costly sponsored large size RCTs, will enrich the literature and broaden the transfer of medical knowledge for better treatment of individuals. Further, MacLehose et al (141), in evaluating the effect size derived from randomized and nonrandomized studies, concluded that discrepancies for high quality studies were small, but that discrepancies for low quality studies were large. In another assessment, Sacks et al (142) examined the inclusion of studies with historical control versus RCTs and found that historical control studies produce effect estimates of larger magnitude. Concato et al (143) showed the effect of meta-analysis based on RCTs versus high quality cohort studies with similar estimates of effect. Benson and Hartz (144), in their 2000 publication, also showed similar results between meta-analysis based on RCTs and on cohort studies performed after 1984. However, Ioannidis et al (145) also found discrepancies in only 8% of the topics covered by prospective studies. Furlan et al (146) showed that discrepant results between cohort studies and RCTs regarding low back pain were almost all attributable to the quality of the studies and to homogeneity. Consequently, well conducted observational studies will yield similar estimates of effect compared with RCTs when bias created by the potential limitations exclusive to observational studies

is small in magnitude compared with the variability and/or bias created by choice of study population, types of subjects willing to enter the study, quality of data acquired, and other random effects. Wang and Schoenbaum (147), describing opportunities and limitations in assessing treatment effects by using analysis in the context of the American Recovery and Reinvestment Act of 2009 (15) and comparative effectiveness research, described that the application of observational, quasi experimental, and other non-experimental methods may also be important in this endeavor. However, they also cautioned that such methods are inherently susceptible to various types of potential bias and thus present special challenges in the search process and with generalizable evidence. Bluhm (148) described multiple other advantages of nonrandomized studies including longevity and the size of the trial compared to randomized trials. She summarized that even though the clean randomized trials identified as "best evidence" on the hierarchy of evidence are important and useful, they do have limitations.

Thus, there is varying evidence that observational studies with nonrandomized designs are part of evidence-based medicine. It is also essential, however, to improve the reporting quality of these types of studies.

The standards for evaluating the body of evidence for each outcome include the systematic assessment of risk of bias, consistency, precision, directness, and reporting bias (4). The systematic review is essentially a tool for managing a vast amount of information generated on the etiology, prognosis, incidence, prevalence, diagnosis, and treatment of disease (4). Over the years, multiple manuscripts have been published about the conduct of systematic reviews and assessment of methodological quality and risk of bias of the included studies (27,28,31,149-172). Similar to the Quality of Reporting of Meta-Analysis (QUORUM) statement (173) and Preferring Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (174), Meta-analysis of Observational Studies in Epidemiology (MOOSE) has been published (28). The Cochrane Back Review Group published Method Guidelines for Systematic Reviews in the field of spinal disorders (175) and updated them (162,176) on multiple occasions, even though these were all limited to randomized trials. West et al (161) described systems to rate the strength of scientific evidence. These systems also described various tools to perform systematic reviews of observational studies.

In addition to the method guidelines for systematic reviews, it has been recommended that RCTs and observational studies be conducted according to substantial guidance by Consolidated Standards of Reporting Trials (CONSORT) (177-179) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (163). Similarly, Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) and Strengthening the Reporting of Observational studies in Epidemiology (STROBE) (27,29) have been described to assess the methodological quality and the risk of bias of nonrandomized or observational studies.

It is essential to find the balance for using observational studies in the era of randomized trials (180). It is well established that RCTs may constitute the gold standard for the generation of evidence-based medicine, but observational studies are also essential. Thus, instruments to assess methodological quality and bias are essential.

More recently, Newcastle-Ottawa Quality Assessment Scales have been utilized (181). The Newcastle-Ottawa Quality Assessment Scale is described separately for case control studies and for cohort studies. These criteria have been used in multiple systematic reviews prepared for the American Society of Interventional Pain Physicians (ASIPP) guidelines (1,2). Recent Cochrane Review criteria (162) have been described as not representing various subspecialties appropriately including IPM. Consequently, Bicket et al (19) have described a separate quality assessment instrument for epidural injections. Furthermore, a quality instrument has been developed for interventional techniques by the ASIPP for randomized trials only (182). While multiple factors influence the quality of study assessment including bias assessment, it is crucial in IPM that the techniques be rated appropriately. Consequently, our objective is to develop a unique tool for the assessment of the methodological quality of nonrandomized or observational studies for interventional techniques with the modification of the instrument developed for randomized trials with incorporation of various qualities of nonrandomized studies (182).

Methods

In this manuscript, we report the development of an IPM specific instrument for the assessment of the methodological quality of nonrandomized studies of interventional techniques.

Methodological quality has been defined as the extent to which all aspects of a design and conduct of the studies can be shown to protect against systematic bias, nonsystematic bias, and inferential error (161).

For the purpose of developing this instrument, we defined the quality to be the extent to which a study's design, conduct, and analysis have minimized selection, measurement, and confounding biases, developing an objective instrument to assess the quality reflecting this definition.

An observational study is defined as an etiologic or effectiveness study using data from an existing database, a cross sectional study, a case series, case-control design, a design with historical controls, or a cohort design (183).

Nonrandomized Controlled Trials

A nonrandomized controlled trial is an experimental study in which people are allocated to different interventions using methods that are not random (30). The observations in a nonrandomized controlled trial may be made before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not. This is called "control before and after study." In contrast, interrupted-time-series or historically controlled studies use observations at multiple time points before and after an intervention. The design attempts to detect whether the intervention has had an effect significantly greater than any underlying trend over time.

Cohort Study

A cohort study is a study in which a defined group of people are is followed over time in order to examine associations between different interventions received and subsequent outcomes (30). A prospective cohort study recruits participants before any intervention and follows them into the future.

A retrospective cohort study identifies subjects from past records describing interventions received and follows them from the time of those records.

Case-Control Study

A case-control study compares people with a specific outcome of interest (cases) with people from the same source population, but without that outcome (controls), to examine the association between outcome and prior exposure (e.g., having an intervention). This design is particularly useful when the outcome is rare.

Cross-Sectional Study

A cross-sectional study collects information on interventions (past or present) and current health outcomes (i.e., restricted to health states) for a group of people at a particular point in time, to examine associations between the outcomes and exposure to interventions.

Case Series

A case series is an uncontrolled longitudinal study where observations are made on a series of individuals, usually all receiving the same intervention, before and after an intervention, but with no control group.

A non-randomized trial is very similar to a randomized trial except for randomization. Some of the prospective nonrandomized trials also include blinding.

Methodologic Quality Assessment Instrument

Methodological quality has been defined as "the extent to which all aspects of the design and conduct of the studies can be shown to protect against systematic bias, nonsystematic bias, and inferential error" (161). Quality is based on the study's design, conduct, and analysis that have minimized selection, measurement, and confounding biases with assessment of specific requirements for interventional techniques. The design of various quality appraisal tools have been described (151-153). Among the multiple quality appraisal tools, some have used numeric scoring systems to rank individual studies with an overall quality score (150,151,155). However, there is an ongoing discussion in relation to the importance of each item and weighing of the scores (156-160). Cochrane methodological review criteria or risk of bias assessment have also have also changed over the years, with numeric scoring systems… included or omitted (19,31,162,173,175,176,184-190). Multiple modifications and the application of self-impressions, by experts results in conclusions and recommendations which may be inappropriate (1,2,6,9,20,49,190-196). It has been recommended that each item on a quality appraisal tool be considered separately for its impact on the quality of the trial rather than relying on an overall quality score (156,159,160). Thus, for the development of the present scoring system for interventional techniques, we sought to use numeric scoring for each individual item and for the total score of items. Item generation was based on the definition of quality as the extent to which the design and conduct of the trial were congruent with the objectives of the trial, whereas applicability was defined as the extent to which the trial procedures could be applied to the contemporary IPM techniques.

The primary investigator (LM) produced a list of 26 individual items designed to investigate each of

the principles. After discussions with 2 other investigators (JH, RB), they were reduced to 20. Each item was explained with references for justification. This list was circulated to the reference group with instructions to indicate if each item should remain on the list, and to decide on appropriate numeric scoring for each item. The reviewers received basic written instructions for the instrument. Each item on the checklist can be rated as "yes," "no," or "unclear" and certain items can be rated as not applicable. The responses from the group were collated, circulated, and were discussed via the internet. All conflicts were resolved. A final review and presentation at a guideline meeting revised the language and a total items of 16 were settled as shown in Table 1.

Table 1. *IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.*

I.	**STROBE OR TREND Guidance**	**Scoring**
1.	Study Design Guidance and Reporting	
	Case Report/Case Series	0
	Study designed without any guidance	1
	Study designed with minimal criteria and reporting with or without guidance	2
	Study designed with moderately significant criteria or implies it was based on STROBE or TREND without clear description or the study was conducted before 2011 or similar criteria utilized with study conducted before 2011	3
	Designed with high level criteria or explicitly uses STROBE or TREND with identification of criteria or conducted prior to 2011	4
II.	**DESIGN FACTORS**	
2.	Study Design and Type	
	Case report or series (uncontrolled – longitudinal)	0
	Retrospective cohort or cross-sectional study	1
	Prospective cohort case-control study	2
	Prospective case control study	3
	Prospective, controlled, nonrandomized	4
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 100 participants without appropriate sample size determination	0
	At least 100 participants in the study without appropriate sample size determination	1
	Sample size calculation with less than 50 patients in each group	2
	Appropriate sample size calculation with at least 50 patients in each group	3
	Appropriate sample size calculation with 100 patients in each group	4
6.	Statistical Methodology	
	None	0
	Some statistics	1
	Appropriate	2
III.	**PATIENT FACTORS**	
7.	Inclusiveness of Population	
7a.	For epidural procedures:	

Table 1 (cont). *IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.*

	Poorly identified mixed population	1
	Poorly identified mixed population with large sample (≥ 200)	2
	Clearly identified mixed population	3
	Disorders specific trials (i.e. well defined spinal stenosis and disc herniation, disorder specific, disc herniation or spinal stenosis or post surgery syndrome)	4
7b.	For facet or sacroiliac joint interventions:	
	No specific selection criteria	1
	No diagnostic blocks based on clinical symptomatology	2
	Selection with single diagnostic blocks	3
	Selection with placebo or dual diagnostic blocks	4
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or less for epidural or facet joint procedures, etc., and 6 months for intradiscal procedures and implantables	1
	3-6 months for epidural or facet joint procedures, etc., or one year for intradiscal procedures or implantables	2
	6-12 months for epidurals or facet joint procedures, etc., and 2 years or longer for discal procedures and implantables	3
	18 months or longer for epidurals and facet joint procedures, etc., or 5 years or longer for discal procedures and implantables	4
IV.	**OUTCOMES**	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	2
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	Description of Drop Out Rate	
	No description despite reporting of incomplete data or more than 30% withdrawal	0
	Less than 30% withdrawal in one year in any group	1
	Less than 40% withdrawal at 2 years in any group	2
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	No groups or groups dissimilar with significant influence on outcomes	0
	Groups dissimilar without significant influence on outcomes	1
	Groups similar	2
14.	Role of Co-Interventions	
	Dissimilar co-interventions or similar co-interventions in some of the participants	1
	No co-interventions or similar co-interventions in majority of the participants	2

Table 1 (cont). *IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.*

V.	**ASSIGNMENT**	
15.	Method of Assignment of Participants	
	Case report/case series or selective assignment based on outcomes or retrospective evaluation based on clinical criteria	1
	Prospective study with inclusion without specific criteria	2
	Retrospective method with inclusion of all participants or random selection of retrospective data	3
	Prospective, well-defined assignment of methodology and inclusion criteria (quasi randomization, matching, stratification, etc.)	4
VI.	**CONFLICTS OF INTEREST**	
16.	Funding and Sponsorship	
	Trial included industry employees with or without proper disclosure	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement or no information available	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
TOTAL MAXIMUM		**48**

Analysis of Data

Each response option was recorded as a category, including unclear and not applicable. Data were analyzed for intraclass correlation coefficient (ICC) derived from a 2-way random model with absolute agreement. An ICC is measured on a scale of 0 to 1, 1 presents perfect reliability, whereas 0 indicates no reliability (197). The kappa statistic, sensitivity, specificity, and predictive positive and negative values were calculated to measure agreement. Kappa (198) is a chance corrected measure of inter-rater reliability and ranges from minus 1 to plus 1, with plus 1 being perfect agreement, minus 1 being perfect disagreement, and 0 being agreement no better than chance. In this study, kappa was interpreted as unreliable ($\kappa < 0.00$), poor ($\kappa = 0.01 – 0.20$), fair ($\kappa = 0.21 – 0.40$), moderate ($\kappa = 0.41 – 0.60$), good ($\kappa = 0.61 – 0.80$), and very good ($\kappa = 0.81 – 1.00$). A 95% confidence interval for kappa was computed using the test-based standard error. For this study, reliability was considered acceptable if it was moderate or higher. All computations were performed using SPSS statistical software version 22 (IBM, New York, NY, USA).

Review of Data

The primary investigator (LM) reviewed all the available instruments, along with the instrument developed for assessment of RCTs (161,181,182). Following this, a list of 28 individual items were designed to investigate each of the principles. After early discussions with other investigators, these items were reduced to 20. Each item was explained with references for justification. The list was circulated among the authors and reviewers. Subsequently, the list was reduced to a total of 18 items.

After the initial assessment of multiple studies by all the participants, 4 manuscripts (199-202) were provided to all the reviewers for scoring. The scores of these manuscripts were considered as final.

Results

As shown in Table 2, inter-rater agreement of IPM-QRBNR criteria was highly variable for individual items. Overall, of the 16 items resulting in a total maximum potential score of 48, 7 items were with an inter-rater agreement of less than 60%. The remaining 9 items showed agreement above 60%.

Discussion

Our purpose was to create a means for assessing the methodological quality of observational or non-randomized studies of interventional procedures. The resulting specialized instrument may also be used for evaluation of pain treatments using implantable devices and disc interventions as well as vertebral augmentation procedures. We conducted an assessment of this instrument with facet joint and epidural injections, 2 of the most common interventional procedures. The reliability of checklist items in the study assessment area of the IPM-QRBNR were evaluated and an inter-rater reliability comparison was done.

Table 2. *Inter-rater agreement of IPM-QRBNR criteria.*

Item no.	Lippitt (201)	MacVicar et al (202)	Ng & Sell (199)	Lee at al (200)	Average Agreement of 4 Trials
1. Study Design Guidance and Reporting	23%	15%	15%	8%	15%
2. Study Design and Type	54%	69%	54%	85%	65%
3. Setting/Physician	92%	54%	100%	100%	87%
4. Imaging	92%	85%	100%	100%	94%
5. Sample Size	31%	92%	61%	85%	67%
6. Statistical Methodology	85%	31%	100%	61%	69%
7. Inclusiveness of Population	54%	69%	92%	77%	73%
8. Duration of Pain	38%	69%	39%	54%	50%
9. Previous Treatments	62%	38%	62%	46%	48%
10. Duration of Follow-up with Appropriate Interventions	61%	62%	69%	54%	62%
11. Outcomes Assessment Criteria for Significant Improvement	38%	85%	54%	31%	52%
12. Description of Drop Out Rate	31%	39%	23%	46%	35%
13. Similarity of Groups at Baseline for Important Prognostic Indicators	77%	62%	31%	62%	58%
14. Role of Co-Interventions	31%	85%	77%	69%	65%
15. Method of Assignment of Participants	85%	54%	77%	38%	63%
16. Funding and Sponsorship	46%	77%	23%	23%	42%
Total Score					
Agreement for scores of < 32	13	7	7	8	67%
Agreement for scores of ≥ 32	0	6	6	5	33%
Agreement for > 60% of items	54% (7)	77% (10)	69% (9)	62% (8)	69% (9)
Agreement for > 80% of items	31% (4)	31% (4)	31% (4)	31% (4)	15% (2)
Intra-class correlation coefficient (single reviewer absolute agreement)					0.595* (95% CI 0.273, 0.818)

The results showed that the reliability for 14 of the 16 items was either moderate or good. There was an intra-class correlation coefficient of 0.595 (95% CI; 0.273 – 0.818). More than half—56%—of the items had more than 60% agreement among the reviewers. Because of this, we believe this to be a dependable tool for assessing nonrandomized studies of spinal interventional procedures. Systematic reviews rely on such tools in their preparation. Reviewers will now have a new, reliable tool for assessing, rating, and discussing these interventions.

As discussed extensively, Cochrane review criteria are the most commonly utilized criteria for randomized trials. However, there are no such criteria widely utilized and reliable for nonrandomized or observational studies. In general it has been described that the majority of experts involved Cochrane reviews were quality assessment content experts rather than clinical experts. There was no involvement of interventional pain physicians. Consequently, this led to the exclusion of observational studies from the analysis. As described earlier, high quality, nonrandomized studies may yield appropriate results and further improve the credibility of the results of randomized trials. It may be argued that nonrandomized studies may also confuse the clinical picture for purists, even though clinically they not only ignite discussion, but also may provide a balanced view. It is commonly believed that the quality assessment of content experts may be biased by prior opinions. Thus, it may be desirable to have not only content experts, but also clinical experts and nonexperts with a methodological background to assess the quality of the studies.

This instrument is unique in that it uses extensive criteria derived from Cochrane review criteria (162) and an instrument developed for RCTs (182). The extensive

assessment of multiple segments of the study are not only practical, but also improve the quality of reporting, study design, outcomes assessment, and conflicts of interest, the most important aspect to be considered in recent years. Multiple factors need to be considered in the interpretation of any new instrument, including the present one, as well as with its application. This is the first such instrument developed for nonrandomized studies describing interventional techniques. Thus, reviewers certainly will face some difficulties with instantaneous understanding of the instrument. It is believed by the authors of this instrument that once the learning curve has passed, reviewers will become comfortable, they will appreciate the substantial insights provided by this instrument.

Assessment of individual items was provided with clarity for interventional techniques. The following descriptions show the background and rater agreement for scoring for the final 16 items included in IPM-QRBNR.

I. ADHERENCE TO STROBE OR TREND GUIDANCE

Item 1: Study Design Guidance and Reporting

Adherence to STROBE and TREND guidelines is crucial. Critical appraisal of the quality of any observational study is possible only if the design, conduct, and analysis of the study is thoroughly and accurately described in the report. Von Elm et al (29) showed that in published observational research, important information is often missing or unclear. An analysis of epidemiological studies published in general medical and speciality journals showed that the rationale behind the choice of potential confounding variables was very infrequently reported (203-205).

Similar to STROBE, multiple other manuscripts and the TREND statement showed the importance of improving the reporting quality of nonrandomized evaluations (27).

The STROBE describes how many questions in medical research are investigated in observational studies such as research into the cause of diseases relying on cohort, case controlled, or cross sectional studies (29). Observational research should be reported transparently so that readers can follow what was planned, what was done, what was found, and what conclusions were drawn. Furthermore, transparent reporting is also needed to judge whether and how results can be included in systematic reviews. Analysis has shown that in published observational research important information is often missing or unclear. Based on the development of CONSORT and its role in the improvement of reporting RCTs, the STROBE statement a checklist of items that should be addressed in articles reporting on the 3 main study designs of analytical epidemiology, was developed. The STROBE statement is a checklist of 22 items that were considered essential for good reporting of observational studies. Multiple extensions of STROBE have been identified in the assessment of other studies (206,207).

The TREND statement was published in 2004 for improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions (27). The TREND emphasizes transparency or clarity in the reporting of individual studies as the key. Sufficient detail and clarity in the report allow readers to understand the conduct and findings of the intervention or study, and how the study was different from or similar to other studies in the field. The HIV/AIDS Prevention Research Synthesis (PRS) team of the Centers for Disease Control and Prevention (CDC) found that many study reports failed to include critical information such as intervention, timing, and dosage, effect size data necessary for research synthesis (208-212). The TREND presents with a checklist of 22 items meant to be consistent with the CONSORT checklist for the reporting of RCTs, and to be used in expanding the information requested by CONSORT for RCTs of behavioral and public health interventions. TREND incorporates some of the questions which are not included in CONSORT.

da Costa et al (206) assessed uses and misuses of the STROBE statement in a bibliographic study. Notwithstanding the clear statement of the purpose of the STROBE by its authors, some journal editors are concerned that the STROBE recommendations may be inappropriately used as an assessment tool to judge the quality of a study, or that researchers may use STROBE as a guideline to set up or conduct observational studies (213). However, only 10% of the 32 observational studies were considered inappropriate. Among 19 systematic reviews, 53% used STROBE inappropriately as a tool to assess study quality. The authors concluded that the STROBE reporting recommendations are frequently used inappropriately in systematic reviews and meta-analysis as an instrument to assess the methodological quality of observational studies.

Sanderson et al (214) also identified and reviewed 86 tools.. The results showed that one-third of the tools were designed for single use in a specific review

and one-third for critical appraisal. They showed that most tools included items for selection method (92%), measurement of study variables (86%), design-specific sources of bias (86%), control of confounding (78%), and use of statistics (78%), and only 4% addressed conflict of interest. The Newcastle-Ottawa scale (181) was used in this assessment, as well as multiple tools assessing the accuracy of diagnostic studies. Despite the extensive review, they were reluctant to recommend a specific tool without having implemented them all on multiple studies for the purpose of assessing their properties and ease of use.

West et al (161) provided an evidence report for systems to rate the strength of scientific evidence. The assessment also included systems for rating the quality of individual articles – observational studies. 16 systems concerning observational studies were assessed to arrive at a set of high performing scales or checklists pertaining to observational studies. The 5 key domains were considered including the comparability of subjects, exposure or intervention, outcome measurement, statistical analysis, and funding or sponsorship. However, the authors were unable to evaluate and recommend which system is most appropriate for the task being undertaken. These findings once again illustrate the lack of appropriate methodology to assess observational studies specifically in settings of IPM.

In this instrument, we have focused significantly on the trial design with a provision of a numeric value of 4 when the study uses explicitly STROBE or TREND criteria with identification of items. A score of 3 is provided when the study implies it was based on STROBE or TREND without clear descriptions. A study design utilizing other than STROBE or TREND criteria is provided with a score of 2. A study design without any significant guidance is provided with a score of 1, whereas case report or case series is provided with a score of 0.

Consequently, in this instrument, we have focused significantly on the study design with providing a numeric value of 3 for a prospective controlled nonrandomized study, with 2 for a prospective cohort or case-control study, 1 for a retrospective cohort or cross-sectional study, and 0 for a case report or series.

II. DESIGN FACTORS

Multiple design factors involved in observational studies are crucial in the analysis of the evidence and the value of that evidence. These include study design, setting where the procedure is performed, type of physician performing the procedure, type of imaging utilized, sample size calculation, and statistical methodology.

Item 2: Study Design and Type

The World Health Organization (WHO) defines a clinical trial as, "any research study that prospectively subjects human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" (215). Observational studies are defined as etiologic or effectiveness studies using data from an existing database, a cross-sectional study, a case series, case-control design, a design with historical controls, or a cohort design (183). Furthermore, observational studies consist of nonrandomized controlled trials,experimental studies in which people are allocated to different interventions using methods that are not random. A cohort study is a study in which a defined group of people is followed over time to examine the association between different interventions received in subsequent outcomes. A case-control study compares people with specific outcomes of intent interest (cases) with people from the same source population, but without that outcome (controls), to examine the association between outcome and prior exposure. A cross-sectional study collects information on interventions past or present as well as current health outcomes. Finally, a case report or case series is an uncollected longitudinal study where observations are made on a series of individuals. Nonrandomized trials specifically conducted prospectively can be as rigorous as randomized trials except for randomization. Some prospective trials that are not randomized also include blinding. All types of observational studies, however, including nonrandomized controlled trials lack placebo control. They can of course have active-control without randomization. Since in IPM it is extremely difficult to design a pure randomized placebo-controlled trial, the rigorous prospective trials may be equivalent to active-controlled randomized trials if performed appropriately with a large number of participants. However, the same issues related to active RCTs in reference to interpretations may be faced in prospective nonrandomized studies. One of the major advantages of prospective or observational studies is local anesthetics which may be significantly effective or as effective as or even better than steroids will not be considered as placebos in the observational studies (1-19,216-232). In addition, the issues related to the effects of placebo, nocebo, and pure and fake placebo are not relevant in observational studies (1,2).

Item 3: Setting/Physician

When assessing a study's quality, it is important to know where and by whom a procedure is performed (2,17). Well trained physicians in IPM settings show the most positive results (17,32-34,36,216-238). Studies performed by a general physician in a general setting often have many problems with design and results reporting and consequently were assigned a score of 0. The next step up in quality are those studies performed by a specialty physician (e.g., anesthesia, orthopedics, neurology, neurosurgery, physical medicine and rehabilitation [PMR]) in a specialty setting. Although not ideal, significant improvement is seen, so a score of 1 is given to them. The highest score, 2, is given to IPM settings with well-trained interventionalists because this setting is the most ideal with proper assessment and procedure protocols.

Training and certification for IPM physicians are accomplished through fellowship training and appropriate board certification, such as pain medicine subspecialty certification from the American Board of Medical Specialties (ABMS) or the American Osteopathic Association, or board certification from the American Board of Interventional Pain Physicians (ABIPP).

Item 4: Imaging

Interventional techniques rely on imaging. Some procedures, such as facet joint injections and transforaminal epidural injections, require imaging for them to be done properly. Despite this, some physicians have performed these and other interventional procedures without imaging guidance in spite of reported disadvantages (2).

Interventional procedures performed blindly are given a score of 0. Procedures are also performed under ultrasound, despite there being little evidence regarding ultrasound's accuracy (34,239-246) even though some claim ultrasound is as accurate as fluoroscopy. Ultrasound is not recommended for spinal procedures, but may be used for cervical sympathetic blocks, peripheral nerve blocks, intraarticular injections, and plexus blocks. Therefore, a score of 1 is given for procedures performed under ultrasound.

Computed tomography (CT) is sometimes used for interventional procedures. Celiac plexus block is the only interventional procedure for which CT is specific. Bui and Bogduk (247) reported that CT lacked effectiveness for transforaminal epidural injections. Further, Atluri et al (248) in assessing transforaminal epidural injections and related complications with fatalities showed an unusually high number of complications with CT-guided procedures. Significant radiation exposure and other side effects make CT-guided procedures require considerable physician time and facility expense (249-251). As a result, a score of 2 is given for procedures performed under CT guidance.

Since fluoroscopy is the most appropriate imaging modality for interventional procedures, it is given a score of 3.

Item 5: Sample Size

Previous or pilot studies form the basis for calculating future sample sizes. On some occasions, however, this may not be appropriate. Some trials have sample sizes so small it is not easy to assess their results. Small sample sizes may be acceptable for randomized interventional studies (252,253); however, observational studies require large populations.

Sample size scoring is as follows: fewer than 100 in a group and no appropriate sample size determination—0; at least 100 patients in a study without appropriate sample size determination—1; at least 50 in each group with appropriate sample size determination—2; sample size of at least 50 in each group—3; and at least 100 in each group with appropriate sample size determination—4.

Item 6: Statistical Methodology

Statistical methodology is important for nonrandomized studies as shown in MOOSE, STROBE, and TREND and for randomized studies in as shown in Cochrane methodological review criteria as well as PRISMA, SPIRIT, CONSORT, and QUOROM (19,20,27-30,163,173,174,177,178). It was decided to add statistical methodology as an analysis item.

III. PATIENT FACTORS

Item 7: Inclusiveness of Population

A study's population is clinically relevant to assessing methodological quality and bias risk. A score of 1 is given for studies reporting poorly identified mixed populations; a score of 2 is given for studies including ≥ 200 patients with a large sample size; a score of 3 is given for a clearly identified mixed population; and a score of 4 is given to studies examining a specific disorder that has well defined limitations (e.g., spinal stenosis, disc herniation).

In order to eliminate false positives and realize good outcomes, therapeutic criteria selection is impor-

tant for facet joint and sacroiliac joint interventions. Diagnostic blocks' usefulness is the subject of debate when the standard is a single or dual block with 50% to 80% pain relief. Nevertheless, the literature reports that dual diagnostic blocks with 75% pain relief predict a significant superiority for therapeutic interventions (2). Therefore, a score of 1 is given when no specific selection criteria were utilized. A score of 2 is provided with use of selection criteria; a score of 3 is given when a single diagnostic block is performed; and a score of 2 is given when dual diagnostic or placebo controlled blocks were performed.

Item 8: Duration of Pain

IPM patient outcomes depend on pain duration and can confuse final outcomes. A patient with acute pain often has a better response than a patient with chronic pain, in both control and intervention groups. As the period of pain extends, the natural regression or progression of the causative disease will often result in a minimization of the pain. Confounding factors such as placebo response and the Hawthorne effect can have the same result. Acute or subacute pain patients often respond better than chronic pain patients. Most pain resolves within 3 months; after 3 months is considered chronic pain. When a study includes patients with pain for less than 3 months or with pain from 3 to 6 months, the results are biased toward the disease's natural progression.

Inclusion of patients with pain of less than 3 months duration was provided with a score of 0, 3 to 6 months was provided with a score of 1, or greater than 6 months was provided with a score of 2.

Item 9: Previous Treatment

Knowledge of past treatments before having an interventional procedure is important. Sometimes conservative management or co-interventions can help, even if they do not provide total relief. A score of 0 is given if patients had not received any treatment; a score of 1 is given if patients had received periodic treatments; and a score of 2 is given if all patients had received structured therapy.

Item 10: Duration of Follow-up with Appropriate Interventions

Documenting follow-up time is important in interventional procedure studies. Studies only reporting 3 months of follow-up do not provide useful information, despite the large numbers of studies that report this follow-up duration. A score of 1 is given if follow-up is 3 months or less for epidural or facet joint injections or 6 months for intradiscal procedures or implantables; a score of 2 is given if follow-up is more than 6 months for epidural or facet joint injections or one year for intradiscal procedures or implantables; a score of 3 is given if follow-up is more than one year for epidural or facet joint injections or 2 years or more for intradiscal procedures or implantables; and a score of 4 is given if follow-up is more than 2 years for epidural or facet joint injections or 5 years or more for intradiscal procedures or implantables.

IV. OUTCOMES

Item 11: Outcomes Assessment

Assessing outcomes is important in IPM. Pain relief is the primary outcome while function is the secondary outcome. Traditionally, functional outcomes have fluctuated wildly; small changes were considered significant (254-260). More robust measures for assessing significant functional improvement exist (2,216-232,237,238,261,262).

In fact, the Cochrane Back Review Group (CBRG) guidelines also provided a set of component outcomes for low back pain trials (263,264). Deyo et al (263) and Bombardier (264) made recommendations for standardized measures to facilitate comparison of results among studies and ensure more complete reporting of relevant outcomes. Further, they recommended psychometrically sound instruments for investigators who have sufficient resources to collect and analyze such data utilizing the Oswestry Disability Index (ODI) or the Roland-Morris Disability Questionnaire to measure functional status.

A Delphi survey of 63 experts from 14 countries, many of whom were members of the Cochrane Back Review Group, was conducted with the intent to arrive at a consensus for reporting back pain trials outcomes (265). The consensus they reached was that continuous patient-reported outcomes, including 95% confidence intervals, should include the following: between group mean differences, the percentage that improve or deteriorate according to established and relevant minimally important change thresholds, and the number needed to treat. The survey participants believe their efforts will facilitate outcomes reporting consistency and improve study results' interpretations.

Considerable discussion about outcomes inside and outside the CBRG has been held (266-269). CBRG au-

thors and editors have looked at the meaning of clinically meaningful change on back pain outcomes that are important to patients (270).

Pain and functional status cutoffs for minimally important change were proposed by Ostelo et al (270). They reviewed the available literature concerning the most common ways to measure minimally important changes. They looked at values found for minimally important change, and conferred with colleagues and experts in the field. A 30% improvement from baseline was determined to be a clinically meaningful improvement. Unlike specific quantitative clinical outcomes such as blood pressure or cholesterol levels, they believe that guidance such as this is important for clinicians to have when measuring pain improvement.

CBRG says they now have a better understanding of pain interventions' effects and their magnitude (31). Despite this, they recognize that there is a paucity of empirical evidence on minimally important change and they hope to pursue further research in this area (31).

Multiple authors have examined and reported weaknesses with minimally important changes and minimally clinical important differences (MCID) (254-257). The rise and fall of the "minimum clinically important difference" was reported by Carragee. MCID's definition is the smallest score differential in a certain domain which is regarded by a patient to be beneficial; this difference would require a change in treating the patient if adverse effects and prohibitive costs would not be incurred. Quoting Shakespeare, Carragee claims that this definition traditionally has been more honored in the breach than in the observance. According to Copay et al (258), MCIDs do not correlate among different measurement techniques. An MCID method based on expert consensus was challenged by Gatchel and Mayer (259). This method advocated the MCID threshold to be a > 30% improvement in subjective patient reports. In the workers' compensation population they examined, using this MCID does not show a relationship to objective health care utilization work status extended outcomes. Parker et al (260) looked at MCIDs after revision fusion for symptomatic pseudoarthrosis in the following domains: pain, disability, and quality of life. Based on how the MCID was calculated, wide variations were discovered—as much as 400%; as low as 2 points on the ODI and 3 points on the SF-12.

These various calculation methods, as well as the wide variations and low values shown, call into question MCID's validity. This is particularly true when measuring heterogeneous disease or patient groups with multiple psychosocial confounders. Gatchel et al (256) looked at a consensus-based MCID threshold's validation. This MCID's threshold used an objective functional external anchor. They found that after treatment there was a 30% or greater self-reported improvement that was significantly associated with physical function improvement on progressive isoinertial lifting. Manchikanti et al, while conducting multiple trials, reported outcomes in neck and back pain of at least 50% improvement and a 40% – 50% disability improvement (216-232,237,238).

Gauging CBRG's effect on clinical practice is worth examining. CBRG is a good source for evidence from which clinical back pain guidelines can be developed. However, there are some noteworthy problems with CBRG, including complicated reviews; limited opportunities to perform a Cochrane review, especially for spine-related disorders; the high cost of their guidelines, either from their Web site or journals where they are published; and the limited availability of the journals in which they are published. CBRG is also saddled with faulty guidance from the American Pain Society (APS) (6,20,192-194). Other deficiencies include using manuscripts prepared for the Bone and Joint Decade Task force on neck pain (271,272) and Dutch guidelines (273).

Outcome assessment criteria for significant improvement varied from 0 to 4. Zero with no description of outcomes or less than 20% change in pain rating or functional status, whereas significant improvement with pain and function of 50% or greater or 3 points and 40% reduction in disability scores earned a score of 4.

Item 12: Description of Dropout Rate

Dropout rate is well described for randomized trials; however, it has not taken a significant role in observational studies, although dropout rate along with a description of how it was accounted for is crucial for observational studies also. A zero score is provided if the incomplete data or more than 30% withdrawal rate is not addressed, less than 30% withdrawal in one-year in any group is provided with a score of 1 and less than 40% withdrawal at 2 years in any group is provided with a score of 2.

Item 13: Similarity of Groups at Baseline for Important Prognostic Indicators

The similarity of groups at baseline for important prognostic indicators is important in randomized trials, however, for observational studies it has not been

described. A score of 0 is provided when there were no groups or groups dissimilar with significant influence on outcomes were shown, groups dissimilar without significant influence on outcomes despite significant influence on outcomes was provided with score of 1, and groups similar was provided with a score of 2.

Item 14: Role of Co-Interventions

The role of co-interventions for interventional techniques is crucial. Almost all patients do receive some type of co-intervention. It is important to keep the co-interventions similar in both groups; however, in the groups, individuals may differ to the extent of their activities and work status, etc. These were not considered as co-interventions. Continued structured interventions and required drug therapy, if provided to all participants in the group, were considered as appropriate.

If the study provided dissimilar co-interventions or similar co-interventions in only some of the participants, it was a score of 1, whereas, if there were no co-interventions or similar co-interventions in majority of the participants the score was 2.

V. ASSIGNMENT

Item 15: Method of Assignment of Participants

The method of assignment of participants is described both in STROBE and TREND statements. Assignment should describe eligibility criteria for participants, including criteria at different levels and recruitment and method of recruitment based on either referral, self-selection, etc., including the sampling method. Recruitment settings including the location must be described.

Participants should be described in each type of study. For a cohort study, the eligibility criteria and the sources and methods of selection of participants must be provided. In addition, methods of follow-up must be described.

For a case-control study, study eligibility criteria and the sources and methods of case ascertainment and control selection should be described, along with the rationale for the choice of the cases and controls.

For a cross-sectional study, eligibility criteria and the sources and methods of selection of participants should be described.

For prospective trials without randomization, the methodology utilized in assigning the patients must be described.

In this assessment of the quality, case report/case series or those reports with selective assignment based on outcomes are provided with a score of 1. A prospective study with inclusion without specific criteria are provided with a score of 2. Retrospective method with inclusion of all participants or random selection of retrospective data are provided with a score of 3. Prospective, well-defined assignment of methodology and inclusion criteria with quasi randomization, matching, or stratification, etc., are provided with a score of 4.

VI. CONFLICTS OF INTEREST

Item 16: Funding and Sponsorship

Critics have put the connection between industry and the research community under the microscope. Journals publish considerable research funded by industry (274-277), but that research is generally of lower quality than research funded by governments, universities, or foundations. Some argue that increasing industry-funded research's scientific quality would result in better evidence quality, thus making the research more valuable for clinical decision-making.

Drug, medical device, and biological makers who take part in federal health care programs are required, per the Affordable Care Act (ACA), to be transparent in tracking and reporting specific payments and items of value received from them by physicians and teaching hospitals (278,279). These reports are required to be sent annually to the Centers for Medicare and Medicaid Services (CMS). These manufacturers, as well as group purchasing organizations, are required to disclose certain ownership interests held by physicians and their immediate family (278,279).

A number of published manuscripts have linked industry sponsorship to more positive outcomes. One, Lundh et al (280), reported flattering risk ratios, harm results, efficacy, and conclusions more often when the study was sponsored by industry. Lundh et al (280) also reported that of 48 papers examined, 5 industry-sponsored studies had larger effect sizes compared to studies not sponsored by industry; no difference in effect size was found in 5 papers. Amiri et al (281) looked at funding sources and conflicts of interest and how they influence the quality of spinal research and reported outcomes. Of the 1,356 papers they identified, 864 met their criteria for assessment. They found a significant correlation between a study's funding source and its outcomes. Bhandari et al (282) also found the association between finding and funding source with industry-

funded trials more likely to be associated with positive findings for both medical and surgical interventions. The relationship between industry funding with outcomes and the quality of rheumatoid arthritis drug therapy RCTs was evaluated by Khan et al (283). They found no association between industry funding and a greater probability of positive outcomes for the drug being studied. They also found that industry-funded RCTs were more likely to have an adequate participant flow, double-blinding, and intention to treat analysis.

Despite mixed findings and opinions, significant pro-industry bias seems to be the general consensus. Current assessment tools do not take industry bias into account; the tool being described in this manuscript will reflect the role of funding and sponsorship in assessing methodological quality.

In addition to industry funding, other types of conflicts of interest have been debated. Editors, authors, and peer reviewers all have been given advice and guidance (274-277,284-310). A conflict of interest is not limited to just sponsorship and funding. Industry funding previously has been funneled through a government agency and ultimately to medical societies conducting studies.

Funding and sponsorship assessment for conflicts of interest included rating as high as 3 and also -3 if the trials included industry employees with or without proper disclosures.

Limitations of this assessment include a difficult learning curve, the final assessment included only 4 studies, even though it was assessed by a large number of raters for the reliability. Consequently, further evaluation is warranted to assess the reliability of IPM-QRBNR, as it will be utilized in systematic reviews and also in the development of guidelines for interventional techniques.

The development and assessment of this instrument was similar to the instrument developed for randomized trials (182); however, inter-rater reliability was less robust for observational studies compared to randomized trials. Further, the instrument for randomized trials was also shown to be superior in initial assessment to Cochrane review criteria for interventional techniques. This may indicate the lack of interest in observational studies to be included in systematic reviews and guideline preparation.

Conclusion

In this assessment, we presented a new instrument, namely Interventional Pain Management techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR) and assessed its reliability as an assessment tool for methodologic quality and risk of bias of interventional nonrandomized controlled trials. Good reliability and inter-rater correlation was appreciated.

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Conflict of Interest:

Dr. Cohen served as a paid co-investigator on a Department of Defense study. He is also a consultant for Halozyme and Kimberly Clark.

Dr. Benyamin is a consultant and lecturer for Boston Scientific and Kimberly Clark.

Dr. Falco is a consultant for St. Jude Medical Inc. and Joimax Inc.

Dr. Vallejo receives research support from Cephalon/Teva, BioDelivery Sciences International, Inc., Mundipharma Research GmbH & Co., AstraZeneca, Purdue Pharma, LP, and Theravance, and is a consultant for Nevro and Kymberly-Clark.

Dr. Kaye is a speaker for Depomed, Inc.

Dr. Helm is a clinical investigator with Epimed and receives research support from Cephalon/Teva, AstraZeneca, and Purdue Pharma, LP. He has attended an advisory group meeting for Activas.

Dr. Racz is a Consultant for and has family ownership of Epimed International, is a Consultant to Cosman RF Company, and has Medtronic patent issues.

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