Supplemental Content 4
Instrument to Assess Potential For Bias and Confound

Type of bias	Conditions required for minimization of bias.
1. Selection bias	***Risk of bias was minimized from selection of participants to be included in the study.*** • Inclusion/exclusion criteria were sufficiently detailed and explicitly described. • No groups of patients were systematically excluded that were not pre-specified to be excluded. • Must state selection as "all participants, consecutive participants, a random sample of participants," or some other statement assuring unbiased selection of participants from the entire population of participants meeting inclusion criteria. (Eg, "Patients were selected from a hospital emergency department" would be rated as "no" or "unclear" whereas, "All patients from June 1 through July 10th, 2000 were screened for eligibility" would be rated as "yes.") • Numbers and reasons for exclusions were reported. • The restrictions of the study setting would not "by definition" eliminate participants who would otherwise be included. (Eg, the study aimed to include all mild TBI/Concussion and the setting was a post-trauma rehab clinic; the setting would not allow for an unbiased selection of mild TBI patients.)
2. Bias due to missing data: • ***attrition*** • ***exclusion of data*** • ***non-responders***	***Risk of bias was minimized from missing data.**** • The overall and differential levels of patient exclusions did not exceed 20% overall or 10% differential. • Patient exclusions did not appear related to SSDs. • Rate of non-responders was low. • Differences between included and excluded participants, or between responders and non-responders was analyzed and groups were similar. (Eg, if the non-responder [or missing data, or study decliner] rate is relatively low AND the analysis examines and accounts for differences between groups, then rate "yes" for low risk of bias.") ***Applies only to data from participants who were included in the study.***
3a. Ascertainment bias related to case definition and identification	***Risk of bias was minimized from case definition and identification.*** • Diagnostic criteria were explicitly described/defined. • Diagnostic criteria were applied equally to the selection of cases vs non-cases. (Eg, a publication in which clear criteria for "a case" were specified [such as GCS of 13-15 at time of injury], and that states the criteria were applied equally to determine who did and did not meet inclusion criteria for the study, would be rated as "yes" for low risk of bias.) • Those who identified cases were trained and/or qualified to do so.
3b. Ascertainment bias related to case assessment	***Risk of bias was minimized by independent and blinded assessment when ascertaining cases.*** • Assessment of cases for diagnosis of concussion or mild TBI was conducted by independent assessors. • Assessment of cases for diagnosis of concussion or mild TBI was conducted by assessors who are blinded to study hypotheses. (Eg, a study that uses ascertainers who are not a part of the research team/athletic team/combat unit AND who are blinded to study hypotheses would be rated "yes" for low risk of bias.

4a. Ascertainment bias related to S/S/D description and evaluation	***Risk of bias was minimized from SSD description and evaluation.*** • Signs, symptoms, neurologic deficits, and neurocognitive deficits (SSDs) were clearly described. • Methods used to evaluate participants for SSDs were clearly described and equally applied. • Those who evaluated participants were trained and/or qualified to do so. (Eg, a study that reports "balance problems" would be rated as "no" for low risk of bias; one that reports neurologists measured balance using a computerized, virtual environment [and describes the testing equipment] would be rated as "yes" for low risk of bias. • <u>For neurocognitive deficits:</u> Instruments used for evaluation of neurocognitive deficits were validated. • <u>For computerized tests:</u> If the computerized test is measuring something objective like reaction time, the test does not need to be validated. However, the technology should be clearly described. If the computerized test is measuring a neurocognitive domain like Attention or Memory, then the test needs to be validated. • <u>For self-reported symptoms:</u> Symptoms are by definition self-reported. If the information is acquired in a managed setting (eg, in a clinical assessment or over the phone by trained telephone assessors), the item would be rated as "yes" for low risk of bias. If the information is acquired in a non-managed setting (eg, a mailed questionnaire), the item would be rated as "unclear" for low risk of bias.
4b. Ascertainment bias related to S/S/D assessment	***Risk of bias was minimized by independent and blinded assessment when evaluating participants.*** • Assessment of participants for evaluation of SSDs was conducted by independent assessors. • Assessment of participants for evaluation of SSDs was conducted by assessors blinded to study hypotheses. <u>For self-report:</u> It must be explicitly stated that participants were unaware of study hypotheses/group assignment for the study to receive a rating of "yes" for low risk of bias.
5. Bias due to confounding	***Risk of bias was minimized by identification and management of potential confounding variables.*** • Participants were their own controls. • Groups were matched. • Groups were statistically determined to be comparable at baseline. • Group differences were statistically accounted for (eg, through covariate adjustment). • Co-morbid and pre-trauma factors were identified and either (a) participants were excluded equally in both groups due to pre-specified co-morbidities and pre-trauma factors, or (b) co-morbidities and pre-trauma factors were adjusted for in the analysis. • Populations from which the PCE group and Control group were selected were similar. (Eg, a study with a PCE group from a hospital emergency ward and a Control group of healthy controls recruited through advertisements would be rated as "no" for low risk of bias.) • If group differences were not examined, or were reported but not accounted for, rate as "no" for low risk of bias. • Studies must, at a minimum, adjust for age and education in all analyses and calculations of test scores. • Need to consider whether the PCE and control samples are drawn from the same population or are similar.

6. Notes	• Outcome reporting bias (authors did not pre-specify outcomes, or only selectively reported results of pre-specified outcomes). • Note the absence of outcome reporting bias if study hypotheses were documented a priori such as in a registered RCT. • Include information if assessment techniques were potentially biased. • Provide any comments that may qualify and/or explain the rating given.
Rating of whether INDIVIDUAL biases were minimized	• **Yes** • **Unclear (not enough information)** • **No**
Ratings of OVERALL potential for bias	• ***Low= "Yes" ratings on all domains, indicating all types of biases were minimized.*** • ***Medium= "No" or "Unclear" on one or more items; flaws raise some doubts about the validity of the results.*** • ***High= "No" on one or more items; flaws seriously weaken confidence in the validity of the results.*** • ***For Item 5 (Confounding): It is possible to give a study an overall rating of "medium" if the rating for Item 5 is "Unclear." It depends upon the population from which the PCE and Control samples were drawn. For example, if a study takes all participants from the same university setting and athletic teams, the need to control for age is less critical than if the study takes participants from hospital E.D. admissions. Similarly, control for co-morbidities could be a fatal flaw in a heterogeneous sample, but less critical in a sample in which the prevalence of co-morbidities is less likely***