Appendix 2: Criteria for class of evidence for MS treatments, adapted from EBSJ 2013.[20]

Class	Bias risk	Study design	Criteria
I	**Low risk** Study adheres to commonly held tenets of high quality design, execution and avoidance bias	Good quality RCT	• Random sequence generation • Allocation concealment • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size • Intent-to-treat analysis
II	**Moderately low risk** Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias.	Moderate or poor quality RCT Good quality cohort	• Violation of 1-3 of the criteria for good quality RCT • Blind or independent assessment in prospective study, or use of reliable data in retrospective study • F/U rate of 80%+ • Adequate sample size • Controlling for possible confounding
III	**Moderately high risk** Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Very poor quality RCT (missing 4 or more of the criteria) Moderate or poor quality cohort Case-control Crossover	• Violation of 4+ of the criteria for a good quality RCT • Violation of any of the criteria for a good quality cohort • Any case-control design • Any crossover design
IV	**High risk** Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Cross-sectional Case series	• Any cross-sectional design • Any case series design