Pooled individual patient data RCTs risk of bias assessment: Fibromyalgia subgroup studies

Study Inputs	
Overall risk of bias summary – input study #1	
Overall risk of bias summary – input study #2	
Overall risk of bias summary – input study #3	
Overall risk of bias summary – input study #4	
Considerations for subgroup interaction in IPD pooled RCT analysis	
Did authors consider inclusion of "across-trial" information? [Fisher, 2011]	
Analytic technique selected, ordered from most to least optimal:[Fisher, 2011] 1. OSM: "one-stage" model with covariate interaction (do authors include a term for trial membership, if this method was chosen?) 2. PWT: pooling of within-trial covariate interaction 3. CWA: "manually" combining separately calculated within- and across-trial effects 4. TCDS: testing for treatment effect differences across covariate subgroups	
Was heterogeneity in interaction effects discussed? (E.g., large I^2 or obvious outlier, or confounding)	
Optimal presentation: were results of interaction effect presented graphically for reader to see (similar to "default presentation style" suggested by Fisher 2011[Fisher, 2011 #4632])?	
Risk of analytic bias based on IPD method for pooled analysis:	[Low, Unclear, High]
Reporting Bias- pooled IPD analysis	
Were all outcomes reported in Results or were only select outcomes reported? (compare to methods section)	
Were results (in tables and/or text) reported for all randomized patients -for main outcomes? -for all outcomes? -for subgroups?	
What is the risk of reporting bias due to selective outcome reporting in pooled analysis?	[Low, Unclear, High]
Additional subgroup items- pooled IPD analysis (adapted from Sun et al.[Sun, 2010 #4677])	
Were subgroups pre-specified (a priori in RCTs) or only for pooled analysis?	
Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? (Skeptical: p>0.01 vs Maybe (0.01<p<0.1) vs p<0.001 Believable)	S-M-B vs NR -or text of "NS"
Is subgroup effect large?	
Is subgroup effect independent? (is another interaction significant for a related variable?)	
Is the interaction effect consistent across similar outcomes in the study?	
Risk of Bias Assessment for pooled IPD methods and reporting	[Low, Moderate or High] and brief rationale (transfer to bottom of this assessment form)

RCT inputs for pooled analysis	
Selection Bias-input RCTs	
Was method of randomization used to generate the sequence described in sufficient detail to assess whether it should produce comparable groups? (inadequate randomization)?	
Were all randomized participants analyzed in the group to which they were allocated? (Intention to treat (ITT))	
Were the groups similar at baseline regarding the most important prognostic indicators?	
Was method of treatment allocation adequate to keep treatment concealed until desired time?(inadequate allocation concealment)	
Risk of selection bias (inadequate randomization or allocation concealment):	[Low, Unclear, High]
Performance Bias-input RCTs	
Was the care provider blinded to the intervention?	Yes, no, NR
Were the participants blinded to the intervention?	Yes, no, NR
Nondrug interventions: Were interventions adequately defined so they could be replicated?	
Was the intended blinding effective?	
Risk of performance bias due to lack of participant and personnel blinding, intervention definition & fidelity to treatment?	[Low, Unclear, High]
Detection Bias-input RCTs	
Were the outcome assessors blinded to the intervention?	Yes, no, NR, NA
Was the scale/tool used to measure outcomes validated, reliable?	
Were co-interventions avoided?	
Was the timing of the outcome assessment similar in all groups?	
Were significance estimates for results appropriately corrected for multiple comparisons?	
Was study adequately powered – To detect main effects? To detect differences in subgroups?	
Risk of detection bias due to lack of outcome assessor blinding, measurement of outcomes, statistical analysis, low study power	[Low, Unclear, High]
Attrition Bias-input RCTs	
Was attrition lower than 20%? -overall -in subgroups	Y, N, NR, NR for SG %
Were reasons for incomplete/missing data adequately explained? -# assessed, -# dropped out, # lost to follow-up, # died	
Were losses to follow-up also reported for subgroups?	
Incomplete data handled appropriately?	
Risk of attrition bias due to amount, nature, or handling of incomplete outcome data?	[Low, Unclear, High]
Reporting Bias-input RCTs	
Were all outcomes reported in Results or were only select outcomes reported (compared to methods section)?	
Were results (in tables and/or text) reported for all randomized patients (vs. only treatment completers) -for main outcomes? -for all outcomes? -for subgroups?	
What is the risk of reporting bias due to selective outcome reporting?	[Low, Unclear, High]

Other Sources of Bias	
Are there other risks of bias? If yes, describe	
Additional subgroup items-input RCTs	
Was subgroup variable measured at baseline or after randomization?	
Were subgroups pre-specified (a priori)?	
Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? Skeptical: p>0.01 vs Maybe (0.01<p<0.1) vs p<0.001 Believable [Sun, 2010 #4677]	S-M-B vs NR -or text of "NS"
Is subgroup effect large?	
Is subgroup effect independent?	
Is the interaction effect consistent across similar outcomes in the study?	
Risk of Bias Assessment for RCT inputs (by outcome)	[Low, Moderate or High] and explanation (1-2 sentences)
Risk of Bias Assessment for pooled IPD methods and reporting (from above)	[Low, Moderate or High] and explanation (1-2 sentences)
Overall Risk of Bias Assessment (by outcome)	[Low, Moderate or High] and brief explanation

Abbreviations: CWA: manually-combining separately calculated within- and across-trial effects; OSM: One-stage model with covariate interaction; PWT: pooling of within-trial covariate interactions; RCT: randomized clinical trial; TCDS: Testing for treatment effect differences across covariate subgroups

References

1. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0: The Cochrane Collaboration; 2011.
2. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions: AHRQ. 2012.
3. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010; 340:c117. 20354011.
4. Fisher DJ, Copas AJ, Tierney JF, et al. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. J Clin Epidemiol 2011; Sep;64(9):949-67. 21411280