Reviewer’s report

Title: Diagnostic accuracy of cardiac MRI, FDG-PET, and myocardial biopsy for the diagnosis of cardiac sarcoidosis: A protocol for a systematic review and meta-analysis

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Reviewer: Francesca Chappell

Reviewer's report:

The authors have written a protocol for a systematic review and meta-analysis of MRI, PET, and biopsy in the diagnosis of cardiac sarcoidosis - a rare but potentially fatal disease. Please note that review is focussed on the statistical aspects as I am not a clinician.

This looks like a very interesting review from a methodological point of view, and I hope the authors obtain the data for all their planned analyses. However, I do have some comments which I hope will improve the manuscript.

1. The Reference Standard does not explicitly say that the Japan Criteria are the reference standard, and I only know that the Japan Criteria are the reference standard as it is stated later on in the manuscript. Also, do the Japan Criteria include the index tests as components? The description suggests imaging but doesn't say whether it is MRI or PET. Also, the clinical pathway flowchart suggests that there would be at least two reference standards - long term follow-up for the patients with normal screening test results and more intensive testing for those with abnormal screening test results. Could the authors please spell out exactly what the reference standard is for all patients and does it include MRI or PET imaging? The authors will know that including the index tests as components in the reference standard is a cause of incorporation bias.

2. There are the criticisms against the Japan Criteria, and this is important. I would not know how to interpret sensitivity and specificity from a study where the reference standard may not be fit for purpose. I can see that this systematic review is interesting from a methodological point of view, but a clinician might question its usefulness. The authors will know that an accurate index test will not have high estimates of sensitivity and specificity if the reference standard is inaccurate.

3. Are there two patient groups? Asymptomatic and symptomatic? Pre-existing extra-cardiac sarcoidosis and "established isolated cardiac sarcoidosis" [page 9 lines 28-29]? If they are including patients with established cardiac sarcoidosis then the sensitivity and specificity estimates will not be clinically applicable - to get a clinically applicable estimate you need a clinically applicable sample, i.e. people in need of a diagnosis, not those who already have one. I would have thought that difference patient groups could require separate analyses.

3. Types of studies - the authors haven't said that they will exclude case-control diagnostic studies (also sometimes called "two-gate" designs). These studies are known for their tendency to overestimate sensitivity and specificity (and I believe that one of the co-authors has written a paper on this very topic). Case-control diagnostic studies recruit patients known to have the disease already, so my comment above about using data from patients with an established diagnosis of cardiac sarcoidosis applies here.
4. I find the analysis plan ambiguous (please note that I am a native speaker of English). What do they mean by, "Part 1: A direct comparison of both CMR and 18F-FDG (separately) as index tests to the reference standard Japan Criteria." To me, the phrase "direct comparison" in this context means using data from studies with a head-to-head comparison of CMR and PET, i.e. studies with results from the same patients from the Japan Criteria, CMR, and PET in one statistical model. So why, "separately"? If they are analysing the data separately, how is this different to the next planned analysis, "An indirect comparison of both CMR and 18F-FDG as index tests to the reference standard Japan Criteria"? Re the analyses with biopsy, is this MRI and biopsy versus PET and biopsy, or MRI and biopsy versus PET, or MRI versus PET and biopsy? There is more detail for the analyses a few paragraphs later, but the whole description could be clearer.

5. Re Part 4 (the Bayesian meta-analysis with informative priors), this looks interesting, but I would like the authors to present the prior and posterior distributions so that the influence of the prior over the posterior can be judged. Prior distributions for the variance and correlation parameters can be particularly problematic, so please include these and not just the priors and posteriors for the sensitivity and specificity parameters.

6. How are they going to assess the adequacy of their statistical models? I can't find much on this.

7. How are they going to edit the QUADAS-2 tool for their review? E.g. instead of "Was there an appropriate interval between index test(s) and reference standard?", something like, "Was the interval between index and reference standard less than 1 month?"

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