

**Author's response to reviews**

**Title:** Diagnostic delay for giant cell arteritis. A systematic review and meta-analysis

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Dear Dr Marinelli,

Many thanks to you for the opportunity to resubmit our work 'Diagnostic delay for giant cell arteritis. A systematic review and meta-analysis' (word count: 3,107) for publication as a Research Article in BMC Medicine. Furthermore, can I give my thanks to the reviewers for their positive and helpful comments in relation to the initial submission (BMED-D-17-00224). Below we have outlined how we have addressed each of the reviewer's points. Please also accept the two accompanying manuscript versions, one of which highlights the specified changes and it is to this one that page and line numbers refer.

Yours sincerely,

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Reviewer #1 Carlo Selmi: In this manuscript, Dr. Prior and Colleagues report on a systematic literature review and meta-analysis to ascertain the diagnostic delay in giant-cell vasculitis. The study is highly meritory and based on very solid methods. The message is very clear (and quite scary).

I would only suggest some minor changes.

First, I feel the manuscript could be shortened to provide a major stress to the underlying message.

- As requested by the reviewer we have tried to reduce the word count where possible, although because of the need for accurate reporting of the methodology and findings in a systematic review and meta-analysis it is difficult to reduce further. Whilst we have reduced text, when addressing the reviewers helpful comments the word count has largely remained unchanged.

Second, I would recommend discussing the possible role of test availability (as for ultrasonography or PET/CT) as confounding factor.

- Page 13, line 255. Though not in the specific context of confounding, we have included text highlighting that delay may also be dependent upon to the availability of services which vary by region.

Third, are there data on the outcomes of delays, particularly as for vision loss?

- Though in the literature poor outcomes (i.e. vision loss) are frequently referred to as being more likely as a consequence of delay, this has rarely been supported by evidence. However, Patil et al (2015) did report that sight loss was significantly reduced in those GCA patients seen through a Fast-track clinic compared to usual care, though reduced delay was one of several likely factors to have influenced this improved outcome. The existing sentence referring to this study in the introduction has been expanded upon (Page 5, Line 56).

Reviewer #2 Susan Lester: This manuscript describes a meta-analysis of the delay between symptom onset and diagnosis in Giant Cell Arteritis (GCA). This is of relevance because of the risks of stroke and blindness with untreated GCA.

The meta-analysis is meticulous and the paper is very well written. However, the meta-analysis does have a number of serious limitations, including the definition of diagnostic delay (which is a complex outcome, with many moving parts), treatment of the outcome variable as a normally distributed variable (when clearly it is not), a very high between-study heterogeneity and consequently extremely wide prediction intervals with values  $< 0$ . Collectively these issues hinder interpretability and generalisability of the results, however, without individual patient data, these issues are largely beyond the author's control. I found the author's consideration of these issues in the Discussion to be excellent, and I agree with their assessment that, in spite of the imperfections, the study does indeed provide useful "benchmarking" data.

- We very much appreciate the reviewers' balanced consideration of the strengths and limitations of this research. We agree that unfortunately there are several limitations we cannot rectify, but are pleased that you feel these are outlined and explained appropriately. Hopefully we (and other researchers) can begin to address such limitations in study designs when examining GCA.

Minor comments:

Despite including the relevant "between-study" variables in Table 1 & 2, the authors make no comment as to whether sampling period, healthcare setting, or the requirement for a positive TAB, had any influence on the between study heterogeneity.

- Page 14, line 287. We have now expanded on these points within the limitations section.

Although mentioned in the Abstract, there was no mention in the Discussion of "Fast Track" clinics for GCA and the reduction in diagnosis time they may realistically achieve with currently available diagnostic techniques

- As per reviewer 1 comment, info on fast-track clinics has been expanded upon in the introduction and we have also aligned the conclusions in the abstract and discussion (Page 15, line 305).