PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Systemic immunomodulatory treatments for atopic dermatitis: protocol for a systematic review with network meta-analysis
AUTHORS	Drucker, Aaron; Ellis, Alexandra; Jabbar-Lopez, Zarif; Yiu, Zenas; Arents, Bernd; Burton, Tim; Spuls, Philip; Küster, Denise; Schmitt, Jochen; Flohr, Carsten

VERSION 1 – REVIEW

REVIEWER	George Lenon RMIT University, Australia
REVIEW RETURNED	09-Apr-2018

GENERAL COMMENTS	Would be good to include a discussion and conclusion section to the end of the paper.

REVIEWER	Chang Ook Park Department of Dermatology, Yonsei University College of Medicine
REVIEW RETURNED	17-Apr-2018

GENERAL COMMENTS	This protocol is well-written.

REVIEWER	Sinéad Langan London School of Hygiene and Tropical Medicine, UK
REVIEW RETURNED	21-Jun-2018

GENERAL COMMENTS	This protocol is a welcome development in a field with major developments but many uncertainties. The authors have gathered the best team possible to answer the research questions using modern methods. I fully support this work being done. My only comments relate to three aspects: 1. As I understand, the authors are planning to use aggregate data from published papers rather than individual patient data for the network meta-analysis. Would it be worth trying to get the individual-level data where possible? This may be particularly important if there is high drop out rates or covariate imbalance. 2. There was a lack of detail around how adverse event data will be extracted and analysed and captured- I realise it is totally dependent on reporting in the original trial, but worth considering 3. The authors have described 16 weeks and greater as long term, and in the context of a disorder which can be lifelong, I thought this warranted comment.

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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Would be good to include a discussion and conclusion section to the end of the paper.

Thank you for this comment. When writing our protocol manuscript, we followed the style set forth in the *BMJ Open* author instructions, which did not include a discussion section for protocol submissions. We do agree, though, that a summary would be helpful at the end of the manuscript and so have added this.

Reviewer 2

This protocol is well-written.

Thank you for affirming our work.

Reviewer 3

This protocol is a welcome development in a field with major developments but many uncertainties. The authors have gathered the best team possible to answer the research questions using modern methods. I fully support this work being done.

Thank you for affirming the importance of our work.

1. As I understand, the authors are planning to use aggregate data from published papers rather than individual patient data for the network meta-analysis. Would it be worth trying to get the individual-level data where possible? This may be particularly important if there is high drop out rates or covariate imbalance.

The reviewer makes an excellent point that individual patient data can be very useful in strengthening network meta-analyses. In a methodological study, incorporating individual patient data in NMA was found to increase the precision of effect estimates (Leahy et al. Res Synth Methods. 2018). However, it was found to not change treatment rankings. While we agree that it would be useful, we fear that obtaining patient-level data will not be possible for the vast majority of trials. No trial, to our knowledge, have made individual patient data publically available. For some older trials, the data may no longer exist. For newer trials, pharmaceutical companies who own the data may not want to share it if they worry our analysis will rank their intervention lower than desired. For these logistical reasons, we have decided not to include individual patient data in the analysis, but we have added this as a future direction in the manuscript ("Study Records" subsection).

2. There was a lack of detail around how adverse event data will be extracted and analysed and captured- I realise it is totally dependent on reporting in the original trial, but worth considering

This is an excellent point by the reviewer. We will likely be faced by heterogeneous reporting of not only the efficacy outcomes but the safety outcomes as well. Given that we are interested in two relatively broad but specific safety outcomes (withdrawal due to adverse events and serious adverse events), we will focus on reporting of these outcomes. We have added a discussion of this to the "Outcomes" subsection of the manuscript.

3. The authors have described 16 weeks and greater as long term, and in the context of a disorder which can be lifelong, I thought this warranted comment.

We agree that, relative to the natural course of atopic dermatitis, 16 weeks is quite short. We chose this cutoff as most trials report results at 12-16 weeks. We have added an acknowledgment of the limitations of our definition to the subgroup and sensitivity analyses" subsection of the manuscript.

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VERSION 2 – REVIEW

REVIEWER	Sinéad Langan LSHTM, UK
REVIEW RETURNED	20-Jul-2018

GENERAL COMMENTS	I appreciate the authors comments and careful responses. I'm not sure I would be so pessimistic about the possibility of individual patient data as increasing these data are required to be available. Certainly worth trying.

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