PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Treatment preferences for preventive interventions for rheumatoid arthritis: Protocol of a mixed methods case study for the Innovative Medicines Initiative PREFER project.
AUTHORS	Falahee, Marie; Simons, Gwenda; DiSantostefano, Rachael; Valor Méndez, Larissa; Radawski, Christine; Englbrecht, Matthias; Bywall, Karin; Tcherny-Lessenot, Stephanie; Kihlbom, Ulrik; Hauber, Brett; Veldwijk, Jorien; Raza, Karim

VERSION 1 – REVIEW

REVIEWER	Finckh, Axel University Hosp Geneva
REVIEW RETURNED	02-Jan-2021

GENERAL COMMENTS	This manuscript describes a protocol of a study that aims to compares two preference elicitation methodologies in pre-clinical RA. The results should inform the development of recommendations for conducting preference studies. MAJOR COMMENTS • None MINOR COMMENTS • The forth bullet on page 5 (“Strengths and limitations of this study”) is not correct. The reviewer knows about at least one or two other studies of preferences for preventive treatments for RA involving confirmed first degree relatives of patients with a clinician confirmed diagnosis of RA. • Page 6, line 45: This reviewer finds the claim that there is “considerable” research in the field of pre-clinical treatment of RA overstated. While there have been a couple of RCTs exploring this paradigm (which have been by the way generally negative or disappointing), and a few others are ongoing, but tend to struggle recruiting. I would call this field ‘emerging’, not one that benefits from ‘considerable research’ effort … • Page 6, line 48-9: While EULAR has issued points to consider for terminology of pre-clinical stages for RA, it has never recommended or identified specifically groups that would be appropriate for prospective trials. Please consider rephrasing.

REVIEWER	Stamm, Tanja Medical University of Vienna, Center for Medical Statistics, Informatics and Intelligent Systems
REVIEW RETURNED	11-Jan-2021

GENERAL COMMENTS	he protocol is well written und describes an interesting and important study on the treatment preferences for preventive interventions for rheumatoid arthritis. The methods are well described and I have only minor comments. - The authors could consider including a flow chart to better describe the phases and timelines of the study. - Why are focus groups and surveys not conducted in all three participating countries? - Should there be a co-author from Romania on the protocol? - How will the patients be selected for the focus groups?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comment 1:
This manuscript describes a protocol of a study that aims to compares two preference elicitation methodologies in pre-clinical RA. The results should inform the development of recommendations for conducting preference studies.

Response:
The authors thank the reviewer for recognising the value of the study described in this protocol.

Minor comment 1:
The forth bullet on page 5 ("Strengths and limitations of this study") is not correct. The reviewer knows about at least one or two other studies of preferences for preventive treatments for RA involving confirmed first degree relatives of patients with a clinician confirmed diagnosis of RA.

Response:
The authors agree there are two existing studies of preferences of first-degree relatives of patients with a clinician confirmed diagnosis of RA, though unlike the present study these include small sample sizes (N=30 and N=32). We have revised the bullet point to reflect this by adding the underlined text as follows: "This is the first quantitative study of preferences for preventive treatments for rheumatoid arthritis (RA) involving a large sample of confirmed, rather than self-reported, first degree relatives of patients with a clinician confirmed diagnosis of RA."

Minor comment 2:
Page 6, line 45: This reviewer finds the claim that there is "considerable" research in the field of pre-clinical treatment of RA overstated. While there have been a couple of RCTs exploring this paradigm (which have been by the way generally negative or disappointing), and a few others are ongoing, but tend to struggle recruiting. I would call this field 'emerging', not one that benefits from 'considerable research' effort …

Response:
The authors accept the reviewer's comment and have changed "considerable" to "an emerging" in the manuscript to address this. The authors agree that recruitment of first-degree relatives in prospective/preventive studies is challenging, and suggest that this further underlines the need for preference studies of this kind to understand decision making of those at risk in relation to preventive treatment. Such understanding could facilitate efficient recruitment in future trials and inform the clinical translation of prediction and prevention studies. This study will also provide information about the extent to which the preferences of first-degree relatives reflect those of a survey panel asked to imagine the same hypothetical scenario. This is important, as if they are comparable, recruitment via survey panels is simpler and less resource intensive.

Minor comment 3:
Page 6, line 48-9: While EULAR has issued points to consider for terminology of pre-clinical stages for RA, it has never recommended or identified specifically groups that would be appropriate for prospective trials. Please consider rephrasing.

Response: The authors agree that the EULAR guidelines refer to the terminology to be used in prospective studies, rather than specifically identifying groups that are appropriate for such trials. We have therefore rephrased the manuscript accordingly to: “EULAR recommendations identify terminology to describe groups of participants appropriate for prospective trials”.

Reviewer: 2

Comment 1: The protocol is well written und describes an interesting and important study on the treatment preferences for preventive interventions for rheumatoid arthritis. The methods are well described and I have only minor comments.

Response: The authors thank the reviewer for this positive comment and are encouraged that the reviewer finds this study both interesting and important.

Minor comment 1:
The authors could consider including a flow chart to better describe the phases and timelines of the study.

Response: The authors thank the reviewer for this helpful suggestion to improve our manuscript. We have added a flowchart (Figure 1) to provide a summary of the study as suggested.

Minor comment 2:
Why are focus groups and surveys not conducted in all three participating countries?

Response:
The survey phase of this study takes place in all three countries. The authors agree that it would be informative and interesting to conduct focus groups across countries. In fact, we originally intended to do this, but it will unfortunately not be possible due to unforeseen personnel changes. However, as the key objective of the qualitative phase is to inform attribute selection for the DCE study, the extended study team (including researchers and patient partners in Germany) agreed that a ranking survey in Germany and Romania to confirm the attributes prioritized as a result of the UK focus groups would be sufficient to finalize the DCE survey.

Minor comment 3:
Should there be a co-author from Romania on the protocol?

Response: No investigators from Romania were included in the study team. The decision to include a Romanian sample was taken after the inception of the PREFER project to enhance the ability of this study to inform understanding of preference variability across populations. Access to the sample for Romania was via an international survey panel rather than via clinical or University sites.

Minor comment 4:
How will the patients be selected for the focus groups?

Response: No patients participate in the focus group study. Participants who are members of the

public are identified via online research recruitment platforms and community message boards. First degree relative participants are invited to take part by their relative who has a diagnosis of RA. Study packs are provided to patients attending rheumatology outpatient clinics, who are invited to pass on the study invitation to their relatives. We have clarified this in the manuscript by adding the underlined text below:

“Members of the general population will be invited to the focus group through an advert on community message boards and online research recruitment platforms. FDRs will be recruited indirectly, through patients with RA identified at outpatient clinics at participating sites. Patients with RA attending rheumatology clinic will be invited to pass on a study invitation to their first degree relatives.”

Editor(s)' Comments 1:
Please include the study design (mixed methods) in the title.

Response: Thank you for highlighting this oversight. We have revised the study title to: “Treatment preferences for preventive interventions for rheumatoid arthritis: Protocol of a mixed methods case study for the Innovative Medicines Initiative PREFER project.”

VERSION 2 – REVIEW

REVIEWER	Stamm, Tanja Medical University of Vienna, Center for Medical Statistics, Informatics and Intelligent Systems
REVIEW RETURNED	11-Feb-2021

GENERAL COMMENTS	Thank you for answering my comments!