

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A randomized, open-label trial to assess the optimal treatment strategy in early diffuse cutaneous systemic sclerosis: the UPSIDE Study protocol
AUTHORS	Spierings, Julia; van Rhenen, Anna; Welsing, Paco; Marijnissen, Anne; De Langhe, Ellen; Del Papa, Nicoletta; Dierickx, Daan; Gheorghe, Karina; Henes, Joerg; Hesselstrand, R.; Kerre, Tessa; Ljungman, P; van de Loosdrecht, Arjan; Marijt, Erik; Mayer, Miro; Schmalzing, Marc; Schroers, Roland; Smith, Vanessa; Voll, Reinhard; Vonk, Madelon; Voskuyl, Alexandre; de Vries-Bouwstra, Jeska; Walker, Ulrich A.; Wuttge, Dirk; van Laar, Jacob

VERSION 1 – REVIEW

REVIEWER	Rong Xiao The Second Xiangya Hospital, Central South University, China
REVIEW RETURNED	22-Oct-2020

GENERAL COMMENTS	In this study protocol, the authors provided a clear rationale and study plan of HSCT versus Immunosuppressive medication in early dcSSc. As the authors discussed, HSCT has been more and more widely adopted in the treatment of SSc. However, it's still a relatively new treatment. This proposed trial may indeed provide more evidence for the implementation of HSCT in dcSSc.
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REVIEWER	Lazaros I Sakkas Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa 41 110, Greece
REVIEW RETURNED	05-Dec-2020

GENERAL COMMENTS	The authors may consider 6 monthly CyP IV pulses instead of 12 (standard treatment in serious rheumatic conditions), and increase the duration of MMF 3 g/day to at least 18 months Line 32. ACE inhibitor co-administered with bactrimel (cotrixomazole) can elevate serum potassium to dangerous levels and cause serious cardiac arrhythmias line 45:urine spot:protein/creatinine ratio
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REVIEWER	Robert Sandler Sheffield Teaching Hospitals UK
REVIEW RETURNED	07-Dec-2020

GENERAL COMMENTS	The authors propose a methodologically sound, and appropriately ambitious study to address an important question within the treatment of a rare and often devastating illness.
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	<p>I wish them well with this work, and look forward to publication of the results.</p> <p>My only comment, relating to the reviewer checklist is that there is no mention of the "limitations" of the study in this protocol. In the "Strength and limitations" section, there are only strengths mentioned. I don't see this as a huge problem, assuming limitations are discussed in the final report.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer's comments

Reviewer: 1

In this study protocol, the authors provided a clear rationale and study plan of HSCT versus Immunosuppressive medication in early dcSSc. As the authors discussed, HSCT has been more and more widely adopted in the treatment of SSc. However, it's still a relatively new treatment. This proposed trial may indeed provide more evidence for the implementation of HSCT in dcSSc.

Response:

Thank you for these positive comments about our work.

Reviewer: 2

1. The authors may consider 6 monthly CyP IV pulses instead of 12 (standard treatment in serious rheumatic conditions), and increase the duration of MMF 3 g/day to at least 18 months
Line 32.
2. ACE inhibitor co-administered with bactrimel (cotrixomazole) can elevate serum potassium to dangerous levels and cause serious cardiac arrhythmias
3. line 45:urine spot: protein/creatinine ratio

Response:

1. We would like to thank the reviewer for the suggestion to change the treatment strategy in study arm B. We however decided to leave arm B unchanged as our current strategy will allow us to compare results with previous stem cell transplantation trials in systemic sclerosis.
2. We agree with the reviewer that theoretically serum potassium levels can rise when using this combination of medication. In our experience this complication is extremely uncommon, nevertheless we added a recommendation with regard to potassium monitoring after initiation of ACE-inhibition (P6, L27: Monitoring of blood potassium levels after initiation of ACE-inhibitors is recommended, especially when combined with co-trimoxazole).
3. We changed the word "urine portion" analysis to "urine spot test" (p5, L5: urine spot test (protein/creatinine ratio)).

Reviewer: 3

The authors propose a methodologically sound, and appropriately ambitious study to address an important question within the treatment of a rare and often devastating illness.

I wish them well with this work, and look forward to publication of the results. My only comment, relating to the reviewer checklist is that there is no mention of the "limitations" of the study in this protocol. In the "Strength and limitations" section, there are only strengths mentioned. I don't see this as a huge problem, assuming limitations are discussed in the final report.

Response:

We thank the reviewer for the feedback. We will discuss any limitations in the final report.