Author’s response to reviews

Title: Novel optical spectral transmission (OST) guided versus conventionally disease activity guided treatment: study protocol of a randomised clinical trial on guidance of a treat-to-target strategy for early rheumatoid arthritis

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Dear J. Singh,

Thank you for giving us the opportunity to submit a revision of our manuscript entitled “Novel optical spectral transmission (OST) guided versus conventionally disease activity guided
We would like to thank the reviewers for their constructive comments and suggestions; please find our response to these below. We have revised the manuscript accordingly.

We really think this revision has improved the quality of our manuscript and hope that you now can accept our paper for publication.

Looking forward to your response,

With kind regards,

on behalf of all authors,

Nick Besselink, corresponding author

Response to reviewers

Reviewer 1:
Dear authors Thank you per opportunit of review your manuscript " Novel optical spectral transmission (OST) guided versus conventionally disease activity guided treatment: study protocol of a randomised clinical trial on guidance of a treatto target strategy for early rheumatoid arthritis". I have a questions below: You lose some the time explain about artrites what is very important but it is confuse the aim of this study protocol, "determine the applicability of the HandScan in tight-control and treat to target treatment strategies of early RA patients." Please I suggest rewritten your aim once says about treatment strategies with the use MTX.
We thank the reviewer for the suggestion. If we understand you correctly, you would like to add to our aim the text that the treatment strategies are based on MTX, right? However, our trial is not a drug trial, it is a treat-to-target strategy trial; it is generally accepted amongst rheumatologists that the strategy to achieve the aim quickly (tight-control and treat-to-target strategies) is much more important than the individual drugs used. Moreover, quantification of inflammation using optical spectral transmission (OST) is not at all dependent on the medication used. We feel that the addition to our aim of the text that the treatment strategies are based on MTX would give the false suggestion that our OST results would be dependent on the medication used and that OST cannot be applied for all RA treatment strategies.

Reviewer 2:

Many thanks for inviting me to review this study protocol that evaluates novel optical device versus disease activity guided treatment in guiding clinical management of rheumatoid arthritis. Its an established trial, with the appropriate approvals and is currently recruiting. The only comments on the protocol presented is an error in the primary outcomes stated in the objectives. There there are 2 primary outcomes suggested - the HAQ at 18 months and the change from baseline. Clearly there can only be 1 primary outcome. I note that the study is powered on the baseline to 18 month delta.

Indeed, our aim was not described clearly; we modified the text, at line 107, it now reads:

"The primary outcome is the change in Health Assessment Questionnaire (HAQ) score from baseline to 18 months."

I would also expect to see some detail/description as to the outcome measures used in the methodology.

Thanks for this useful suggestion. Indeed, our customized cost questionnaires and radiographic assessment of damage of hand and wrist joints using a newly developed fully automated radiographic scoring system were not described in detail. We now added details on the radiographic scoring system and the cost questionnaires in the Design – Assessment section, and a reference for the HAQ and for the new scoring system.
Reviewer 4:

This is an important trial comparing two treat-to-target strategies - DAS vs HandScan - in early RA. Recommendations:

The authors might consider bringing the rationale for not using DAS or Boolean remission up-front in the Background or Methods. Currently it is tucked away on Page 12, Paragraph 2, Lines 293-300 of the Discussion.

Thanks for this suggestion. We now mention the rationale in the objectives, at the section describing the primary outcome.

The Treatment Strategy, Escalation Strategy, De-Escalation Strategy and the strategy for dealing with Adverse Events to DMARDS are all well described. However, the authors might consider including a sentence or two on how they plan to deal with potential imbalances in the two arms. Potentially, one or other treatment arm might include an excess of patients switching to LEF from MTX? Page 8, Line 194.

Indeed, imbalances could occur regarding e.g. the use of leflunomide. However, it is generally accepted amongst rheumatologists that the strategy to achieve the aim quickly (tight-control and treat-to-target strategies) is much more important than the individual drugs used. In drug treatment strategies according to a standard (step-up) protocol, differences in drug use can occur but are part of the total strategy. The overall analysis is therefore an intention to treat (ITT) analysis. No specific analysis on use of individual drugs are planned. However, we plan to perform generalized linear models to permit adjustments for covariates (see your suggestion below), in which this imbalance, if it would occur, can be adjusted.

Currently the measures taken to prevent large deviations in HandScan and DAS-Guided treatment are somewhat sketchy - see DASPrevention of Under- and Over-Treatment in the HandScan Arm Page 9, Line 204. More detail is needed where "measures are taken" potentially leading to a switch to the "clinical arm". I thought it was unclear who would be making this decision, what data would be reviewed, when and by whom or by what?
Thanks for this useful suggestion. Indeed, our description was not detailed. The implemented software application allows for logging of current and previous patient-specific input, and thereby switches the patient to the “clinical arm” in the case of three consecutive discrepancies without intervention of the researcher. To clarify this, we changed the order of ‘Implementation of a software application for patient-tailored, tight-control treatment’ and ‘Prevention of under- and overtreatment in the HandScan arm’ and added necessary details.

Missing Data. The authors might consider clarifying Missing Data procedures. Especially, the decision to switch from LOCF to multiple imputation methods. Currently Page 10, Line 244 specifies multiple imputation will be used if >10% of the data are missing. However, this may or may not be appropriate depending upon the patterns of missing data. In addition, the authors state that imputations will be based upon baseline characteristics and known predictors without any a priori statement of those "baseline characteristics" or "known" predictors. A little more detail would be good.

The reviewer is right. We did not mention this, in line with your next recommendation, we changed an analysis to a mixed model analysis to include all patients and correct for prognostic baseline covariates. In this way missing data is handled appropriately as well as is accounted for the repeated measures over time within patients. The covariates mentioned: centre, age, gender, disease activity (DAS28), rheumatoid factor and anti-CCP and HAQ all at baseline are the relevant predictors for the (implicit) imputation in the mixed model analysis.

Page 11, Line 268 restricts the analysis of change from baseline in radiographic scores to Mann-Whitney tests. This seems too restrictive? I'd recommend extending this to "ranks-based methods or generalized linear models" to permit adjustments for covariates.

Thanks for this useful suggestion. We follow your suggestion to also perform generalized linear models/mixed model analysis to permit adjustments for covariates. We added this info to the statistical methods section.

Patient Safety Page 11, Lines 274-283. Early stopping based on AE and potential patient switching seems sensible but there is not detail on the stopping criterion - see Line 277. More detail would be good.
The reviewer is right. We did not go into detail here, but now we added details on this.

Page 13 I recommend that plans be made for anonymized data to be shared in a public repository in accordance with FAIR Guidelines.

Indeed, UMC Utrecht has a strict data management policy, completely compliant with the FAIR data principle. Data of the present study are collected in Research-Online which is also fully compliant with the FAIR data principle, including audit trails.