Author’s response to reviews

Title: Short course daily prednisolone therapy at the time of upper respiratory tract infection in children with relapsing steroid sensitive nephrotic syndrome (PREDNOS 2): protocol for a randomised controlled trial

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Author’s response to reviews: see over
Editors in Chief
Trials

Dear Sirs

Re: MS: 9379553601102842 - Short course daily prednisolone therapy at the time of upper respiratory tract infection in children with relapsing steroid sensitive nephrotic syndrome (PREDNOS 2): protocol for a randomised controlled trial

We would like to thank Dr Cobo for his insightful review of our manuscript and for his helpful comments. We will respond to each of these in turn:

Major Compulsory Revisions
I’m confused about the reference group, the standard of care, the study aims, and the future implications of the PREDNOS trial. From the paper, I understand that the standard of care with those patients (abstract second line and background line 10) is long term prednisolone. So, I was expecting a non-inferior aim of a short regime against the long one (maybe non-inferior efficacy and better safety). But your control group is placebo. If you show differences with placebo, how would you argue that a long regime has to be substituted by your proposed short one? Also, how standard is the long one? How much is it based on evidence? If there are clinical guides for the long regime, is it ethical to randomize to placebo? Please, clarify those points in order to avoid similar doubts for future readers.

Reply:
We sincerely apologise that our manuscript has not explained our study intervention with sufficient clarity. Patients who have relapsing steroid sensitive nephrotic syndrome (SSNS) may be commenced on a prolonged course of a variety of different immunomodulatory therapies to reduce the frequency of their relapses. One of the most commonly prescribed therapies is low dose alternate day prednisolone; here a patient is commenced on e.g. 5 mg of prednisolone on alternate days for perhaps 6-12 months in an attempt to see whether this reduces the number of relapses that they experience. Where this is unsuccessful, other agents, e.g. ciclosporin or cyclophosphamide may be used. Despite these therapeutic interventions relapses still occur, and one of the most common precipitating events is the development of upper respiratory tract infection (URTI); about 50% of relapses are URTI-related. At present, current standard of care in the UK is for no change to be made to immunomodulatory therapy when URTI develops. The PREDNOS 2 study aims to determine whether the administration of a six day course of daily prednisolone given specifically at the time of URTI reduces the risk of a relapse subsequently developing. Patients are randomised to receive either 6 days of daily prednisolone or placebo, commencing at the time of onset of URTI. All long-term immunomodulatory therapy, including low dose alternate day prednisolone, will continue to be administered unchanged throughout the six day course of study drug. Taking the example of the patient described above, receiving long-term prednisolone at a dose of 5mg on alternate days – when URTI develops, commencement of study drug will either 1] increase their prednisolone dose to a total of 15mg/m$^2$ daily for six days (if in the active treatment arm) or 2] result in no change – they will continue on 5mg on alternate days (if in the placebo arm). Treatment is double-blind.
The six day intervention with daily prednisolone (or placebo) at the time of URTI development is, therefore, additional to any background prednisolone (or other) therapy, and does not aim to replace this. The trial is assessing intervention with a six day course of daily prednisolone at time of URTI, rather than long vs. short course.

The evidence of this intervention comes from three studies published to date which suggest that in children with relapsing SSNS from South Asian countries receiving long-term alternate day prednisolone therapy, the use of a five to seven day course of daily prednisolone therapy at the time of URTI is associated with a lower rate of subsequent relapse of nephrotic syndrome than when no such change is made to their therapy (current standard care). PREDNOS 2 is assessing this question in a UK population, since these previous studies had a number of methodological issues, and the results from these studies may not be generalisable to the UK, where the pattern of childhood URTI is significantly different, with lower incidence of fever and general absence of diarrhoea.

We have made a number of changes to the Background section, which we hope, will help to clarify these points.

I’m also confused by the main variable, sample size rationale, statistical analysis and the length of follow up. SS is based on the comparison of the proportion of patients having a relapse. For this, you only need one episode. After this episode, you may finish the follow up and allow a different open treatment for that patient. It is expected that an analysis with more episodes will have more information and more power. Is this extra power needed? Does it justify extra follow up for the patient which has already had an episode? Will recruitment be easier for a shorter follow-up? [If there is a clear treatment policy after the first episode, do we need to know more information? I.e., is it practically relevant if the treatment (or the outcome) of the first episode affects the outcome of future episodes?] Please, clarify.

Reply:
The reviewer is correct that the sample size is based on the first relapse. When we originally submitted this project for funding to the NIHR, our primary outcome measure was the number of relapses over the 1 year follow-up period, because, as suggested by the reviewer, this would provide a more powerful analysis. However, after much discussion with the MCRN Nephrology Clinical Studies Group (the co-applicants), it was felt that capturing the outcome following the first URTI provided the most unbiased assessment of treatment efficacy, as concerns were expressed by the group that using the mean number of relapses over a 12 month follow-up period could result in bias in favour of the placebo arm (see below for explanation).

The study hypothesis is that giving daily prednisolone at time of URTI will reduce the subsequent development of disease relapse. If this hypothesis proves to be correct, then those children randomised to the placebo arm may experience more disease relapses than those children randomised to active drug. The current standard of care for the treatment of relapsing nephrotic syndrome includes the commencement of immunomodulatory therapies, including alternate day prednisolone, ciclosporin and cyclophosphamide, cyclophosphamide and other agents following 2 or more relapses in any 6 month period in an attempt to reduce the subsequent relapse frequency. Since it would be unethical to withhold or delay such intensification of treatment until completion of the 12 month trial follow-up period, and many clinicians would not be happy to do so, treatment intensification, where indicated, has to be allowed within the protocol. However, the implication of this is that by virtue of their increased likelihood of relapsing, children in the placebo arm are possibly more likely to undergo such intensification of immunosuppressive therapy, which then means that the overall likelihood of these children subsequently relapsing is reduced. This could introduce bias into the analysis, with the net result being that the placebo arm would appear more
effective than it actually is. By analysing the data after the first URTI (for the primary outcome), this potential for bias to the main outcome measure is removed.

In previous studies, children whose immunosuppressive treatment was intensified were excluded from the study and data analysis for the reasons outlined above. However, the exclusion of these patients also introduces bias, as the analysis will exclude those children who do badly. In PREDNOS 2, a pragmatic decision was taken to continue to follow-up all patients, as it is not known whether these assumptions hold true, and by excluding these children, bias is also introduced with differential drop-out between the two treatment arms. Therefore, it was decided that all children will be followed up for 12 months to additionally assess the difference in mean relapse rate between the two treatment arms over the 12 month period, and this is considered an important secondary outcome measure.

We will not know whether a 6-day course of daily prednisolone administered at the time of URTI reduces the risk of development of disease relapse until the end of the trial when the results are made available; it is therefore ethical to continue to treat patients according to this study protocol at each URTI over the one year period of follow-up and we will investigate the impact of the intervention on the annual rate of relapse as a secondary end-point. We also do not foresee any problems with following up patients for one year in terms of patient retention. The three-monthly visit schedule is entirely in keeping with the frequency of routine clinical care in children with relapsing SSNS. Further, in the aforementioned PREDNOS study, we are following patients for at least one year, and up to a maximum of 4 years. Retention rates within the linked PREDNOS study are excellent, so we do not foresee any problems with follow-up of patients in the PREDNOS 2 for 12 months, as many of the same centres and clinicians are involved in both studies. Finally, by collecting 12 month data this will provide valuable clinical information on these patients, and allow for a more informative health economic evaluation of these treatment regimens.

Please, in accordance with Trial rules for study protocols, specify that your final report will be published in accordance with the CONSORT statement. Please note that SPIRIT was released last year and it provides you with several chances to improve your design. Of special importance for guaranteeing transparency are items 31a, 31b and 31c, which ask protocol authors to provide details of their dissemination policy. Please, note that the Spirit figure requires your table 1 to highlight that randomization occurs after recruitment.

Reply:
Thank you. We have added a section on dissemination (page 23), which we hope meets with your approval. We can confirm that we have provision within our study funding to allow the purchase of open access for published manuscripts. We have altered Figure 1 and Table 1 to indicate that randomisation occurs after recruitment. We have added the CONSORT And SPIRIT statements to our references.

Minor essential Revisions
Please, specify somewhere your efforts to avoid trial attrition.

Reply:
We have added a short paragraph about subject retention on page 16.

Please, consider rewording the inclusion criteria to make clear which conditions are required for any patient and which ones are alternative conditions for eligibility.

Reply:
Thank you. We have revised the inclusion and exclusion criteria to provide further clarity.
Please, consider justifying the reasons why a similar effect size is expected for the different subgroups described on page 10.

Reply:
It is the opinion of the investigators, a large body of experienced Consultant Paediatric Nephrologists, that there is no reason to believe that the different background therapies which the subjects are receiving will impact on the treatment effect size, though we acknowledge that there is no evidence or data in the literature to support (or refute) this view. We were keen to make our study findings as broadly generalizable as possible, and for this reason chose to include subjects on any background immunomodulatory therapy. We have planned a subgroup analysis for the study to address this very issue – to ascertain whether any difference in treatment effect size between the various groups does indeed exist.

We have made some minor changes to paragraph 1 page 19 to reflect this.

Discretionary revisions
Please, consider either deleting the final background sentence (“…important definitive evidence…”) or substituting it with the more technical first sentence in Methods.

Reply:
Thank you for this helpful suggestion. We have made this change.

Please, consider changing ‘UK’ to ‘developed’ in the last line of the Background section of

Reply:
Thank you for this helpful suggestion. We have made this minor change.

I attach a copy of the revised manuscript – all changes that we have made are marked in bold red font. We trust that our explanations meet with your satisfaction and that the changes that we have made to the manuscript make it now worthy of publication in Trials. We look forward to hearing further from you.

Yours sincerely

Professor Nicholas J A Webb. Chief Investigator

Natalie Ives. Lead Statistician