Short course daily prednisolone therapy at the time of upper respiratory tract infection in children with relapsing steroid sensitive nephrotic syndrome: The PREDNOS 2 Trial

Trial Registration: ISRCTN10900733

Statistical Analysis Plan

SAP Version Number	Protocol Version Number
V2.0	v3.0

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Statistical Analysis Plan (SAP) Amendments

SAP version number	SAP section number	Description of and reason for change	Timing of change with respect to interim analysis/ final analysis/ database lock	Blind Reviewer	
2.0		Review of SAP prior to final analysis, decision made to transfer to new BCTU template which is a more comprehensive document. Text from previous SAP copied over to appropriate sections in new template. New sections in template, uses template text and/or text taken directly from SAP v1.0 or the latest protocol.	Prior to final database lock	Name:	
				Signature:	
				Date:	
	4.3	Following discussion with TSC and funder, the primary outcome was changed from URTI-related relapse following the first URTI to first URTI-related relapse, so URTI-relapse could occur after any URTI during the 12 month follow-up period.			
	4.7	Sample size was revised during study, with the inflation rate applied to the sample size increased from 10-20% to 30%.			
	9.1	The primary analysis will include covariate adjustment of the minimisation variable. Since the SAP was written, there has been a change in practice with the standard now for analyses to be adjusted for the minimisation variables included in the randomisation process.			
	9.3	Text in SAP v1.0 on handling missing data for the secondary endpoints based on continuous data deleted. These outcomes are being analysed using repeated measures methods which can accommodate missing data.			
	9.5	Analysis methods for primary outcome changed to reflect the use of regression models to adjust for the minimisation variables in the analysis.			

		Intervention effect to be expressed as a risk difference and relative risk, rather than an odds ratio.			
	9.6	Analysis methods changed to reflect the use of regression models to adjust for the minimisation variables in the analysis.			
	9.10	Planned per-protocol analysis removed as considered uninformative now the primary outcome changed to any URTI-related relapse during the 12 months rather than assessing for relapse following first URTI, meaning for those who do not experience an URTI-related relapse during the 12 months which URTI is used for the assessment of adherence. Adherence to study medication is being assessed and summarised in a descriptive manner as described in section 7.2.			

Abbreviations & Definitions	
Abbreviation / Acronym	**Meaning**
BCTU	Birmingham Clinical Trials Unit
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSNS	Steroid Sensitive Nephrotic Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
URTI	Upper Respiratory Tract Infection
Term	**Definition**
International Standard Randomised Controlled Trial Number	A clinical trial registry
Protocol	Document that details the rationale, objectives, design, methodology and statistical considerations of the study
Randomisation	The process of assigning trial subjects to intervention or control groups using an element of chance to determine the assignments in order to reduce bias.
Statistical Analysis Plan	Pre-specified statistical methodology documented for the trial, either in the protocol or in a separate document.

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1. Introduction

This document is the Statistical Analysis Plan (SAP) for the PREDNOS 2 trial, and should be read in conjunction with the current trial protocol. This SAP details the proposed analyses and presentation of the data for the main paper(s) reporting the results for PREDNOS 2.

The results reported in these papers will follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (e.g. to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (e.g. transformation of data prior to analysis), but they are intended to establish rules that will be followed, as closely as possible, when analysing and reporting data.

Any deviations from this SAP will be described and justified in the final report or publication of the trial (using a table as shown in Appendix A). The analysis will be carried out by an appropriately qualified statistician, who should ensure integrity of the data during their data cleaning processes.

2. Background and rationale

The background and rationale for the trial are outlined in detail in the protocol. In brief, presenting episodes and relapses of nephrotic syndrome in children with steroid sensitive nephrotic syndrome (SSNS) are treated with high dose prednisolone. At least 50% of relapses are precipitated by viral upper respiratory tract infection (URTI), possibly mediated through release of cytokines.[1] Furthermore, in children with frequently relapsing SSNS, the development of an URTI results in relapse in over 50% of instances. Given these strong links between viral URTI and relapse, and the morbidity and cost associated with relapse and its treatment, it is logical that attempts are made to ameliorate the URTI-driven process.

3. Trial objectives

The primary objective is to determine whether a six day course of oral prednisolone given at the time of URTI reduces the incidence of first URTI-related relapse in children with relapsing SSNS.

Secondary objectives are to determine whether a six day course of oral prednisolone given at the time of URTI:

i. Reduces the overall rate of URTI-related relapse of nephrotic syndrome
ii. Reduces the overall rate of (URTI-related and non URTI-related) relapse of nephrotic syndrome
iii. Reduces the cumulative dose of prednisolone received over the 12 month trial period
iv. Reduces the incidence and prevalence of adverse effects of prednisolone including behavioural abnormalities
v. Reduces the number of subjects undergoing escalation of background immunosuppressive therapy

vi. Increases the number of subjects undergoing reduction of background immunosuppressive therapy
vii. Is more cost-effective than standard therapy

4. Trial methods

4.1. Trial design

PREDNOS 2 is a multi-centre, prospective, double-blind, superiority, parallel group, phase III randomised controlled trial. See Appendix B for trial schema.

Participants will be recruited from secondary care.

4.2. Trial interventions

Active treatment group: Daily prednisolone for a total of 6 days commenced within 24 hours of the criteria for an URTI being met.

Control group: Daily matched placebo for a total of 6 days commenced within 24 hours of the criteria for an URTI have being met.

See protocol for detailed information on the dosing of the study drug.

4.3. Primary outcome measure

The primary outcome is first URTI-related relapse of nephrotic syndrome during the 12 month follow up period.

Relapse is defined as Albustix positive proteinuria (+++ or greater) for 3 consecutive days or the presence of generalised oedema plus 3+ proteinuria.

An URTI-related relapse is defined as a relapse occurring within 14 days of the development of an URTI.

4.4. Secondary outcome measures

The secondary outcomes are as follows:

i. Rate of URTI-related relapse of nephrotic syndrome
ii. Rate of relapse (URTI-related and non URTI-related) of nephrotic syndrome
iii. Cumulative dose of prednisolone (mg/kg and mg/m^2) received over the 12 month period
iv. Incidence of serious adverse events (SAEs)
v. Incidence of adverse effects of prednisolone including assessment of behaviour using the Achenbach Child Behaviour Checklist
vi. Incidence of escalation of background immunosuppressive therapy
vii. Incidence of reduction of background immunosuppressive therapy

viii. Quality of life using the PedsQL (0=worst, 100=best). See Section 9.4 for questionnaire scoring.
ix. Cost per relapse of nephrotic syndrome
x. Cost per QALY gained

The secondary outcomes measures ix and x relate to the health economic analysis and are not part of this SAP.

4.5. Timing of outcome assessments

The schedule of trial procedures and outcome assessments are given in the protocol section 4.12.

4.6. Randomisation

Participants will be randomised in a 1:1 ratio to either active treatment or placebo.

Randomisation will be performed centrally at the Birmingham Clinical Trials Unit (BCTU) using a minimisation algorithm incorporating the following factor:

- Treatment regimen subject is receiving at randomisation: no background immunosuppressive therapy; long term maintenance prednisolone therapy; long term maintenance prednisolone therapy plus other immunosuppressive therapies; other immunosuppressive therapies alone.

4.7. Sample size

A total of 360 subjects will be recruited into the trial (180 into each group).

In children with frequently relapsing SSNS, the development of an URTI results in relapse in around 50% of instances.[2] To detect an absolute difference of 17.5% (i.e. 35% proportional reduction) in URTI-related relapse rate (i.e. from 50% to 32.5%), with 80% power and alpha=0.05, requires 250 subjects in total. Allowing for 30% drop out (e.g. subject withdrawal or lost to follow up, or subject not having an URTI during the 12 month follow up period), will require recruitment of 360 subjects. We therefore propose to recruit 360 subjects, 180 to each group.

4.8. Framework

The objective of the trial is to test the superiority of one intervention to another.

The null hypothesis is that there is no difference in the number of children experiencing an URTI-related relapse between the intervention groups. The alternative hypothesis is that there is a difference between the groups.

4.9. Interim analyses and stopping guidance

A separate Data Monitoring Committee (DMC) reporting template will be drafted and agreed by the DMC including an agreement on which outcomes will be reported at interim analyses. The statistical methods stated in this SAP will be followed for the outcomes included in the DMC report, where possible.

Interim analyses of efficacy and safety are planned annually. The Haybittle-Peto approach will be used whereby all interim analyses use a difference of 3 standard errors (approximately p=0.002) as a stopping guideline. These interim analyses will be reviewed by the DMC on an annual basis or more frequently if required by the DMC or Trial Management Committee

4.10. Internal Pilot Progression Rules

Not Applicable.

4.11. Timing of final analysis

The final analysis for the trial will occur after the last patient randomised into the trial has reached 12 months follow up and the corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This is provided that the trial has not been stopped early for any reason (e.g. DMC advice or funding body request).

4.12. Timing of other analyses

Not Applicable.

4.13. Trial comparisons

All references in this document to 'group' refer to the active 6 day daily course of prednisolone group or to the placebo group.

5. Statistical Principles

5.1. Confidence intervals and p-values

All estimates of differences between groups will be presented with two-sided 95% confidence intervals, unless otherwise stated. P-values will be reported from two-sided tests at the 5% significance level.

5.2. Adjustments for multiplicity

No correction for multiple testing will be made.

5.3. Analysis populations

All primary analyses (primary and secondary outcomes including safety outcomes) will be based on the intention-to-treat (ITT) principle. Participants will be analysed in the intervention group to which they were randomised, and all participants shall be included whether or not they

received the allocated intervention following an URTI. This is to avoid any potential bias in the analysis.

The ITT population will not include all of the randomised population. Analyses will be based on a modified ITT population which will include only those participants who had an URTI over the 12 month follow up period. Excluding those participants who did not have an URTI will result in no bias as taking the study medication is conditional on them experiencing an URTI, and this should by chance be balanced between the two groups.

5.4. Definition of adherence

Adherence to allocated intervention will be monitored using the parent-reported tablet count. This is instead of using the returned pot tablet count because the tablet count is just a check of what they have taken compared to what they have said they have taken, rather than whether or not they have been adherent to the intervention. This is further complicated by reissued pots, pots that have not been returned, dropped tablets etc. Good adherence is defined as participants taking 80-120% of their required tablets.

5.5. Handing protocol deviations

A protocol deviation is defined as a failure to adhere to the protocol such as errors in applying the inclusion/exclusion criteria, the incorrect intervention being given, incorrect data being collected or measured, follow-up visits outside the visit window or missed follow-up visits. We will apply a strict definition of the ITT principle and will include all participants as per the modified ITT population described in section 5.3 for the primary analyses, in some form, regardless of deviation from the protocol.[3] This includes participants who were randomised but later found to not meet the inclusion or exclusion criteria. This does not include those participants who have specifically withdrawn consent for the use of their data in the first instance; however these outcomes will be explored as per other missing responses.

5.6. Unblinding

This is a double-blind trial with the participants and clinicians remaining blind to treatment allocation. To maintain blinding, participants randomised to the control group receive the same number of study tablets that they would have received in the active treatment group through supplemental placebo tablets. The Trial Statistician has been unblinded to the intervention code for all of the interim analyses, and presented unblinded analyses to the DMC.

6. Trial population

6.1. Recruitment

A flow diagram (as recommended by CONSORT[4]) will be produced to describe the participant flow through each stage of the trial. This will include information on the number (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial.

6.2. Baseline characteristics

The trial population will be tabulated with categorical data summarised by number of participants, counts and percentages, and continuous data summarised by the number of participants, mean and standard deviation if deemed to be normally distributed or number of participants, median and interquartile range if data appear skewed, and ranges if appropriate. Tests of statistical significance will not be undertaken, nor confidence intervals presented.[5]

7. Intervention(s)

7.1. Description of the intervention(s)

Not Applicable.

7.2. Adherence to allocated intervention

Adherence to allocated intervention will be summarised descriptively. At each follow-up visit, if the participant had an URTI the following questions are completed:

- Did the parent commence their child on study medication at time of URTI?
- If study medication not commenced, please state reason
- Date study medication commenced (note: study medication should be commenced within 24 hours of the criteria for an URTI being met).
- Was the whole 6 day course of study medication taken?
- If no, how many days were missed?
- Was the 6 day course prematurely discontinued?
- If study medication discontinued, please state reason

These questions will be summarised and presented by group.

8. Protocol deviations

Frequencies and percentages by group will be tabulated for the protocol deviations.

9. Analysis methods

9.1. Covariate adjustment

In the first instance, intervention effects between groups for all outcomes will be adjusted for the minimisation parameter listed in section 4.6. Other covariate adjustment will be baseline values for parameters where available (e.g. an analysis of questionnaire scores will also include the baseline score as a covariate in the model).

If covariate adjustment is not possible (e.g. the model does not converge), the minimisation variable covariate will be removed from the model, but where applicable adjustment for baseline values will still be made. If the model still does not converge, unadjusted estimates will be produced, and it will be made clear in the final report why this occurred (e.g. not possible due to low event rate/lack of model convergence).

If the log-binomial model fails to converge, a Poisson regression model with robust standard errors will be used to estimate the same parameters[6]. If this also fails to converge, unadjusted estimates will be produced from the log-binomial model. It will be made clear in the final report why this occurred (e.g. not possible due to low event rate/lack of model convergence).

9.2. Distributional assumptions and outlying responses

Distributional assumptions (e.g. normality of regression residuals for continuous outcomes) will be assessed visually prior to analysis; although in the first instance the proposed primary method of estimation in this analysis plan will be followed. If responses are considered to be particularly skewed and/or distributional assumptions violated, the impact of this will be examined through sensitivity analysis; this will consist of transformation of responses prior to analysis (e.g. log transformation) in the first instance. If extreme values are apparent and considered to be affecting the integrity of the analysis, a sensitivity analysis consisting of removing the outlying response(s) and repeating the analysis will be performed. Output from these analyses, if performed, will be described and presented alongside the original analysis (or included, e.g. in appendices) with the excluded values clearly labelled.

9.3. Handling missing data

In the first instance, analysis will be completed on received data only with every effort made to follow-up participants even after protocol violation to minimise any potential for bias. To examine the possible impact of missing data on the results, and to make sure we are complying with the intention-to-treat principle, sensitivity analysis will be performed on the primary outcome measure.[7] See section 9.10 for further details regarding sensitivity analyses.

9.4. Data manipulations

The Trial Statistician will derive all responses from the raw data recorded in the database:

Cumulative dose of prednisolone:

Prednisolone is recorded in both Part B1 and Part I of the follow-up form at each time-point. Part I dosing is recorded as free text so in order to use this data for the cumulative prednisolone doses, the Trial Statistician will recode all the free text as the numerical variables: dose and frequency where possible.

Then, in the first instance, clean data from Part B1 and Part I will be combined.

Data can then be checked across both parts of the form to see whether there are any duplicates in doses received. Duplicated doses will be deleted.

Any dosing regimens that are ongoing on one form will be checked against the following form for the stop date. Once a stop date has been obtained, the entry or entries where

the dose is ongoing will be collapsed, so that there is one dose regimen with a defined start and stop date.

There may be some instances where start date and/or stop date are missing as the sites had a rough idea of the treatment regimen but not of the dates e.g. tapering regimen following a relapse. In these cases it is more appropriate to check against the participants relapse history and received treatment in order to make sensible assumptions about the missing dates, than to not use the available data.

If a start date is pre-randomisation date, and the prednisolone regimen is on-going at point of randomisation, the start date will be replaced with the randomisation date so as to only capture prednisolone therapy during the trial.

Cumulative prednisolone dose will be based on those participants who complete the full 12 months trial follow-up. If the dose is ongoing at 12 months the dose will be truncated at 12 months (i.e. randomisation date + 12 months) to provide the cumulative prednisolone dose over the 12 month follow-up period.

For those in the active treatment group, the trial treatment will be included in the cumulative prednisolone. Where tablet count is available, the tablet count will be converted to mg, and then added to the cumulative prednisolone for that participant. If tablet count is not available, then other information on adherence to the trial medication will be used instead to provide an estimated tablet count or dose.

Since drug data is notoriously difficult to collect and analyse, as a check of the statistical code, a manual check and calculation of cumulative prednisolone for 20 participants will be undertaken.

Incidence of Escalation/Reduction of Background Immunosuppressant Therapy:

The background treatment regimen is collected at each of the follow up time points. Data on second line immunosuppressants is also collected (ciclosporin, tacrolimus, levamisole, mycophenolate mofetil, mycophenolate sodium, azathioprine, cyclophosphamide and rituximab). The background treatment regime is categorised into the following four categories:

1. No long-term alternate day prednisolone or other long-term immunosuppressive therapies
2. On long-term alternate day prednisolone only
3. On both long-term alternate day prednisolone and other long-term immunosuppressive therapies
4. On other long-term immunosuppressive therapies only

The background treatment regimen and second line immunosuppressant information will be used in the following way to calculate escalation/reduction of background immunosuppressant therapy:

Escalation will be computed based as per the following criteria –

- If a patient is in category 1 from the background treatment regime at previous visit and then at a following time-point is in category 2, 3 or 4 of the background treatment regime then this is considered as an escalation.
- If a patient is in category 2 from the background treatment regime at previous visit and then at a following time-point is in category 3 or 4 of the background treatment regime then this is also considered as an escalation.
- If a patient is in category 4 from the background treatment regime at previous visit and then at a following time-point is in category 3 of the background treatment regime then this is also considered as an escalation.
- If the participant is not on cyclophosphamide or rituximab at previous visit but are then given cyclophosphamide or rituximab at the following time-point then this is also considered as an escalation.
- If participant has an addition of any immunosuppressant (e.g. addition of ciclosporin) in between follow up visits then this is considered an escalation.
- If the participant has a change in medication from Levamisole to either Tacrolimus, Ciclosporin or Mycophenolate then this is also considered as an escalation.

Reduction will be computed based as per the following criteria –

- If a patient is in category 3 from the background treatment regime at previous visit and then at a following time-point is in category 4, 2 or 1 of the background treatment regime then this is considered as a reduction.
- If a patient is in category 4 from the background treatment regime at previous visit and then at a following time-point is in category 2 or 1 of the background treatment regime then this is also considered as a reduction.
- If a patient is in category 2 from the background treatment regime at previous visit and then at a following time-point is in category 1 of the background treatment regime then this is also considered as a reduction.
- If participant on an immunosuppressant (except cyclophosphamide or rituximab) at one time point, but is no longer on it at the following time point then this is also considered as a reduction.

PedsQL for ages 2-4 years

The PedsQL response scales are coded as follows:

Physical Functioning (problems with…)

- Walking: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Running: : Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Participating in active play or exercise: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Lifting something heavy: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Bathing: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Helping to pick up his or her toys: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Having hurts or aches: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Low energy level: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

Emotional Functioning (problems with…)

- Feeling afraid or scared: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Feeling sad or blue: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Feeling angry: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Trouble sleeping: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Worrying: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

Social Functioning (problems with…)

- Playing with other children: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Other kids not wanting to play with him or her: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Getting teased by other children: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Not able to do things that other children his or her age can do: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Keeping up when playing with other children: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

School Functioning (problems with…)

- Doing the same school activities as peers: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Missing school/daycare because of not feeling well: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Missing school/daycare to go to the doctor or hospital: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

The scores are derived as follows:

- Mean physical functioning score=sum of all physical function scores / (number of items answered)

- Mean emotional functioning=sum of all emotional functioning scores / (number of items answered)

- Mean social functioning=sum of all social functioning scores / (number of items answered)

- Mean school functioning=sum of all school functioning scores / (number of items answered)

NOTE: If more than 50% of items in the scale are missing, a domain score should not be computed for that domain.

Psychosocial Health Summary Score = sum of items in emotional functioning, social functioning, and school functioning scales / (number of items answered)

Physical Health Summary Score = Physical Functioning Scale score (as shown above)

Total score: Sum of all the items / (number of items answered)

PedsQL for ages 5-7 years

The PedsQL response scales are coded as follows:

Physical Functioning (problems with…)

- Walking more than one block: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Running: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Participating in sports activity or exercise: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Lifting something heavy: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Taking a bath or shower by him or herself: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Doing chores, like picking up his or her toys: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Having hurts or aches: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Low energy level: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

Emotional Functioning (problems with…)

- Feeling afraid or scared: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Feeling sad or blue: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Feeling angry: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Trouble sleeping: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Worrying about what will happen to him or her: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

Social Functioning (problems with…)

- Getting along with other children: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Other kids not wanting to be his or her friend: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Getting teased by other children: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Not able to do things that other children his or her age can do: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Keeping up when playing with other children: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

School Functioning (problems with…)

- Paying attention in class: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Forgetting things: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Keeping up with school activities: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Missing school because of not feeling well: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Missing school to go to the doctor or hospital: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

The scores are derived as follows:

Mean Physical Functioning=sum of all physical function scores / (number of items answered)

Emotional Functioning=sum of all emotional functioning scores / (number of items answered)

Social Functioning=sum of all social functioning scores / (number of items answered)

School Functioning=sum of all school functioning scores / (number of items answered)

NOTE: If more than 50% of items in the scale are missing, a domain score should not be computed for that domain.

Psychosocial Health Summary Score = sum of items in emotional functioning, social functioning, and school functioning scales / (number of items answered)

Physical Health Summary Score = Physical Functioning Scale score (as shown above)

Total score: Sum of all the items / (number of items answered)

PedsQL for ages 8-12 years

Physical Functioning (problems with…)

- Walking more than one block: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Running: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Participating in sports activity or exercise: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Lifting something heavy: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Taking a bath or shower by him or herself: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Doing chores around the house: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Having hurts or aches: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0
- Low energy level: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

Emotional Functioning (problems with…)

- Feeling afraid or scared: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Feeling sad or blue: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Feeling angry: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Trouble sleeping: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Worrying about what will happen to him or her: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

Social Functioning (problems with…)

- Getting along with other children: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Other kids not wanting to be his or her friend: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Getting teased by other children: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Not able to do things that other children his or her age can do: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Keeping up when playing with other children: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

School Functioning (problems with…)

- Paying attention in class: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Forgetting things: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Keeping up with schoolwork: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Missing school because of not feeling well: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Missing school to go to the doctor or hospital: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

The scores are derived as follows:

Mean Physical Functioning=sum of all physical function scores / (number of items answered)

Emotional Functioning=sum of all emotional functioning scores / (number of items answered)

Social Functioning=sum of all social functioning scores / (number of items answered)

School Functioning=sum of all school functioning scores / (number of items answered)

NOTE: If more than 50% of items in the scale are missing, a domain score cannot be computed for that domain.

Psychosocial Health Summary Score = sum of items in emotional functioning, social functioning, and school functioning scales / (number of items answered)

Physical Health Summary Score = Physical Functioning Scale score (as shown above)

Total score: Sum of all the items / (number of items answered)

PedsQL for ages 13-18 years

Physical Functioning (problems with…)

- Walking more than one block: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Running: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Participating in sports activity or exercise: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Lifting something heavy: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Taking a bath or shower by him or herself: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Doing chores around the house: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Having hurts or aches: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Low energy level: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

Emotional Functioning (problems with…)

- Feeling afraid or scared: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Feeling sad or blue: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Feeling angry: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Trouble sleeping: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Worrying about what will happen to him or her: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

Social Functioning (problems with…)

- Getting along with other teens: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Other teens not wanting to be his or her friend: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Getting teased by other teens: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Not able to do things that other teens his or her age can do: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Keeping up when playing with other teens: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

School Functioning (problems with…)

- Paying attention in class: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Forgetting things: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Keeping up with schoolwork: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Missing school because of not feeling well: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

- Missing school to go to the doctor or hospital: Never=100, Almost Never=75, Sometimes=50, Often=25, Almost Always=0

The scores are derived as follows:

Mean Physical Functioning=sum of all physical function scores / (number of items answered)

Emotional Functioning=sum of all emotional functioning scores / (number of items answered)

Social Functioning=sum of all social functioning scores / (number of items answered)

School Functioning=sum of all school functioning scores / (number of items answered)

NOTE: If more than 50% of items in the scale are missing, a domain score should not be computed for that domain.

Psychosocial Health Summary Score = sum of items in emotional functioning, social functioning, and school functioning scales / (number of items answered)

Physical Health Summary Score = Physical Functioning Scale score (as shown above)

Total score: Sum of all the items / (number of items answered)

9.5. Analysis methods – primary outcome(s)

The outcome will be presented as number of URTI-related relapses along with percentage using the modified ITT cohort.

An adjusted risk difference and relative risk along with the respective 95% confidence intervals will be estimated using binomial models with the identity and log link respectively. Statistical significance of the treatment group parameter will be determined from the p-value generated by the model. The number needed to treat will also be provided.

See section 9.1 for covariate adjustment and model convergence.

9.6. Analysis methods – secondary outcomes

The number of participants experiencing any relapse (i.e. both URTI-related and non URTI-related relapses), the number of participants having an escalation of background immunosuppressant therapy and the number of participants having a reduction of background immunosuppressant therapy will be presented and analysed as per the primary outcome measure.

The rate of URTI-related relapses and rate of any relapse will be presented in the first instance as numbers of participants who have a relapse with the respective percentage, and in the second instance as a median and IQR. An adjusted incidence rate ratio with 95% confidence interval will be estimated using a Poisson regression model. An offset for the length of time the participant was in the trial will be included in the model. Statistical significance of the treatment group parameter will be determined from the p-value generated by the model.

The cumulative dose of prednisolone received over the 12 month period will be presented as means with standard deviations and ranges. Adjusted mean differences along with 95% confidence intervals will be estimated using a linear regression model. Statistical significance of the treatment group parameter will be determined from the p-value generated by the model.

Adverse effect data will be tabulated at each time point (3, 6, 9 and 12 months) with statistical significance determined by a chi-squared or Fisher's exact test (as appropriate). We will also assess whether or not each adverse event occurred over the whole trial period by assessing all the 3, 6, 9 and 12 month data collectively.

Quality of life measures are taken at multiple time points, as is the Achenbach Behaviour Checklist Scores. Means and standard deviations will be summarised at each time point. Data will be analysed using mixed effect repeated measures models with the minimisation variable and the baseline questionnaire score included in the model as covariates. Time will be included as a continuous variable in the model. In the initial model, a treatment by time cross-term will be included in the model. If this is not significant, it will be considered that the treatment effect

is constant over time, and models without the treatment by time cross-term will be fitted. Adjusted mean differences between groups will be presented alongside the respective 95% confidence interval.

9.7. Analysis methods – exploratory outcomes and analyses

Any data that does not form a pre-specified outcome will be presented using simple summary statistics by intervention group (i.e. numbers and percentages for binary data and means (or medians) and standard deviations (or inter-quartile ranges) for continuous normal (or non-normal) data.

9.8. Safety data

The number and percentage of participants experiencing any adverse events, serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be presented by intervention group. Statistical significance will be determined by a chi-squared or Fisher's exact test (as appropriate). A table listing the SAEs including information on the nature of the event and whether or not it was deemed related to the trial treatment will be provided.

9.9. Planned subgroup analyses

Interpretation of subgroup analysis will be treated with caution (output will be treated as exploratory rather than definitive[9]). Analysis will be limited to the primary outcome only, and the following subgroups based on Background Treatment Regimen at Randomisation:

- No background immunosuppressive therapy; long term maintenance prednisolone therapy; long term maintenance prednisolone therapy plus other immunosuppressive therapies; other immunosuppressive therapies alone.
- On prednisolone vs. not on prednisolone
- On other immunosuppressant vs. not on other immunosuppressant

The effects of these subgroups will be examined by including a treatment group by subgroup interaction parameter in the final binomial model.

9.10. Sensitivity analyses

Sensitivity analyses will be limited to the primary outcome and will consist of:

- URTI-related relapse (Worse) / no URTI-related relapse (Best) and no URTI-related relapse (Best) / URTI-related relapse (Worse) for active and placebo groups respectively.

As an additional analysis, the number of URTI and non-URTI related relapses along with the number of participants who had a relapse in the modified ITT cohort will be compared to the number of non-URTI related relapses in that of the excluded cohort. It would be anticipated that those who have been excluded experience fewer relapses on the basis that they did not experience an URTI. However, if the numbers are similar it might be the case that some URTIs went unreported in this excluded population.

10. Analysis of sub-randomisations

Not Applicable.

11. Health economic analysis

As indicated in the protocol there will also be an economic analysis. The details of this analysis are documented separately.

12. Statistical software

Statistical analysis will be undertaken in the following statistical software packages: SAS software and Stata.

13. References

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6. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6.
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8. THE EUROQOL GROUP. (1990) EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy*, 16, 199-208
9. 7. Wand R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Reporting of subgroups analyses in clinical trials. NEJM. 2007;357:2189-94.

Appendix A: Deviations from SAP

This report below follows the statistical analysis plan dated <insert effective date of latest SAP> apart from following:

Section of report not following SAP	Reason
<insert section >	<insert, e.g. exploratory analyses request by TMG>

Appendix B: Trial schema