PROTOCOL

Full Title: Short course daily prednisolone therapy at the time of upper respiratory tract infection in children with relapsing steroid sensitive nephrotic syndrome

Short Title: PREDNOS 2 study

EudraCT number – 2012-003476-39
MHRA Clinical Trials Authorisation: 21761/0281/001-0001
Ethical Approval: North West GM Central Ref: 12/NW/0766
ISRCTN10900733

Trial Co-Sponsors – Central Manchester University Hospitals NHS Foundation Trust and University of Birmingham
Sponsor's Project Number: RG_12-188

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NIHR Medicines for Children Research Network Nephrology Clinical Studies Group

Protocol Version 2.0 **Date 28th February 2017**

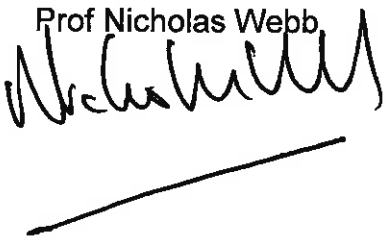
Funding Body: National Institute for Health Research Health Technology Assessment programme: Grant number 11/129/261

Amendments and Chief Investigator Signature

This protocol describes the PREDNOS 2 trial and provides information about procedures for patients taking part in the PREDNOS 2 trial. The protocol should not be used as a guide for treatment of patients not taking part in the PREDNOS 2 trial.

This protocol version has been approved by:

Name: Prof Nicholas Webb **Trial Role:** Chief Investigator

Signature:  **Date:** 8/3/2017

Date of amendment	Protocol version number	Type of amendment	Summary of amendment
22nd Nov 2012	1.1	In response to REC provisional opinion - minor	Typo corrections and addition of CTA, REC and ISRCTN numbers
20th Feb 2014	1.2	Substantial amendment	Amendment to the wording of an exclusion criterion, additional details added to the statistical analysis section, update to the TSC and DMEC members, and other minor and administrative amendments.
9th June 2015	1.3	Substantial amendment	Update to recruitment period and total study duration.
28th February 2017	2.0	Substantial amendment	Update to recruitment period and study duration, amendment to the wording of SAE reporting, amendment to the primary endpoint, update to the data collection section and other minor amendments.

Principal Investigator Declaration

I have read and agree to the current PREDNOS 2 protocol, as described above and understand that any suggested changes to the protocol must be approved by the Trial Steering Committee prior to seeking approval from the Main Research Ethics Committee (MREC) and/or Regulatory Authority.

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki, local regulations (as applicable) and the trial protocol and I agree to conduct the trial according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial.

Principal Investigator Signature

Name: …….

Signature: ……...

Date: ……

Name of Institution

Trust Name: ……

The Principal Investigator should sign this page, file the original copy with the current protocol in the site file, and return a copy to the PREDNOS 2 Trial Office.

PREDNOS 2 Trial Management Group

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Clinical queries during office hours should be directed to one of the Clinical Co-ordinators, or to an appropriate member of the Trial Management Group.

Protocol Synopsis

Title	Short course daily prednisolone therapy at the time of upper respiratory tract infection in children with relapsing steroid sensitive nephrotic syndrome
Short Title	PREDNOS 2 study
Clinical Phase	III
Chief Investigator	Prof Nicholas Webb, Royal Manchester Children's Hospital, Manchester
Trial Co-Sponsors	Central Manchester University Hospitals NHS Foundation Trust and University of Birmingham
Funding	National Institute for Health Research Health Technology Assessment programme (HTA 11/119/261)
Sample Size	360
Accrual Period	5 years and 1 month
Follow-up period	All subjects will be followed up for 12 months
Study Duration	7 years and 1 month
End of Trial Definition	The end of trial will be 6 months after the last data capture. The last data capture will be 12 months following recruitment of the last subject. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trials Office will notify the MHRA and main REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.
Study Design	Double blind randomised controlled trial (RCT)
Aim of Study	To evaluate the effectiveness of a six day course of daily prednisolone therapy at the time of URTI in reducing the development of subsequent nephrotic syndrome relapse in children with relapsing SSNS.
Primary Study Objectives	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 steroid sensitive nephrotic syndrome
Primary Outcome Measures	First URTI-related relapse of nephrotic syndrome during the 12 month follow-up period. Relapse is defined as Albustix positive proteinuria (+++ or greater) for three consecutive days or the presence of generalised oedema plus 3+ proteinuria. URTI-related relapse is defined as a relapse occurring within 14 days of the development of an URTI. First URTI-related relapse refers to the first URTI-related relapse which occurs within the 12 month study follow up period.
Secondary Study	To determine whether a six day course of oral

Objectives	prednisolone given at the time of URTI i] reduces the overall rate of URTI-related relapse of nephrotic syndrome (expressed as relapses per year). ii] reduces the overall rate of relapse of nephrotic syndrome (expressed as relapses per year). iii] reduces the cumulative dose of prednisolone received over the 12 month study 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 (e.g. addition of ciclosporin, tacrolimus, cyclophosphamide etc.). vi] increases the number of subjects undergoing reduction of background immunosuppressive therapy (e.g. cessation of ciclosporin or long term maintenance prednisolone therapy). vii] is more cost effective than standard therapy.
Secondary Outcome Measures	i] Rate of URTI-related relapse of nephrotic syndrome (relapses per year). ii] Rate of relapse (URTI-related and non URTI-related) of nephrotic syndrome (relapses per year). iii] Cumulative dose of prednisolone (mg/kg and mg/m^2) received over the 12 month study period. iv] Incidence of 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 (e.g. addition of ciclosporin, tacrolimus, cyclophosphamide etc.). vii] Incidence of reduction of background immunosuppressive therapy (i.e. cessation of long term maintenance prednisolone therapy). viii] Quality of life using the CHU-9D, EQ-5D and PedsQL. ix] Cost per relapse of nephrotic syndrome. x] Cost per QALY gained.
Inclusion Criteria	Subjects aged over 1 year and less than 19 years will be eligible for inclusion if they have relapsing SSNS, defined as **having experienced 2 or more relapses in the preceding 12 months**. This will include the following groups: • Subjects on no long-term immunosuppressive therapy; • Subjects receiving long term maintenance prednisolone therapy at a dose of up to and including 15mg/m^2 on alternate days. Note that this

	is the maximum dose at the time of recruitment – if children subsequently receive a higher dose e.g. after relapse, they can remain in the study; • Subjects receiving long term maintenance prednisolone therapy at a dose of up to and including 15mg/m^2 on alternate days in conjunction with other immunosuppressive therapies, including levamisole, ciclosporin, tacrolimus, MMF, mycophenolate sodium and azathioprine; • Subjects receiving long-term immunosuppressive therapies, including levamisole, ciclosporin, tacrolimus, MMF, mycophenolate sodium and azathioprine without long term maintenance prednisolone therapy. • Subjects who have previously received a course of oral or intravenous cyclophosphamide: o Must have experienced two relapses in the 12 months prior to randomisation (in keeping with all other subjects) o Must have experienced at least one of these relapses following completion of cyclophosphamide therapy o Must be at least 3 months post completion of oral or intravenous cyclophosphamide therapy • Subjects who have previously received a single dose or course of intravenous rituximab: o Must have experienced two relapses in the 12 months prior to randomisation (in keeping with all other subjects) o Must have experienced at least one of these relapses following completion of rituximab therapy o Must be at least 3 months post completion of intravenous rituximab therapy • Parents and (where age appropriate) subject understand the definition of URTI and the need to commence study drug once this definition has been met. • Written informed consent obtained from the subject's parents/guardians and written assent obtained from subject (where age appropriate). Subjects aged 16 years and above will provide their own written informed consent.
Exclusion Criteria	• Subjects with steroid resistant nephrotic syndrome. • Subjects receiving, or within 3 months of completing a course of oral or intravenous cyclophosphamide. • Subjects receiving, or within 3 months of receiving a course of rituximab. • Subjects on daily prednisolone therapy at time of recruitment.

	• Subjects on a prednisolone dose of greater than 15mg/m^2 on alternate days at time of recruitment. • Subjects with a documented history of significant non-adherence with medical therapy. • Subjects who will be transferred from paediatric to adult services during the 12 month study period. • Subjects unable to take prednisolone tablets, even in crushed form. • Known allergy to prednisolone.
Treatment Description/Arms	Active treatment arm: Daily prednisolone for a total of 6 days commenced once criteria for URTI have been met. Control arm: Daily placebo for a total of 6 days commenced once criteria for URTI have been met. An URTI will be defined as the presence of at least 2 of the following *for at least 24 hours*: • sore throat • ear pain/discharge • runny nose • cough (dry/barking) • hoarse voice • fever >37^oC (measured using tympanometric electronic thermometer) Subjects who are receiving a long term maintenance prednisolone **dose of up to and including 15mg/m^2 on alternate days** (including those not on maintenance prednisolone therapy) at the time of development of URTI will receive the following; Active treatment arm - prednisolone 15mg/m^2 daily for a total of six days, through the use of additional prednisolone study drug tablets. Control arm – No change to therapy through the use of placebo study drug tablets for a total of six days. For example, if a subject is receiving a long term maintenance prednisolone dose of 10mg/m^2 on alternate days, for those subjects randomised to the active treatment arm, the dose will be increased to 15mg/m^2 daily for a total of six days. Those in the control arm will receive prednisolone 10mg/m^2 on alternate days, placebo tablets being administered to increase the total number of tablets so that it is identical to that being administered in the active treatment arm. Subjects who are receiving a prednisolone **dose of greater than 15mg/m^2 on alternate days** at the time of development of URTI will receive the following; Active treatment arm - prednisolone at alternate daily dose given daily for a total of six days, through the use of additional prednisolone study drug tablets Control arm – No change to therapy through the use of placebo study drug tablets for a total of six days.

	For example, if a subject is receiving a prednisolone dose of 30mg/m^2 on alternate days, for those subjects randomised to the active treatment arm, the dose will be increased to 30mg/m^2 daily for a total of six days. Those in the control arm will receive prednisolone 30mg/m^2 on alternate days with a matching number of placebo tablets being administered on the alternate days (3 days) for a total of 6 days. Once the six day course of study drug is complete, the subject will revert to their previous long term maintenance prednisolone dose (or no prednisolone if previously not receiving this). This will be repeated each and every time the subject develops an URTI meeting the designated criteria over the 12 month study period.
Primary Analysis	Incidence of first URTI-related relapse during the 12 month study period.
Secondary Analyses	Comparison between active treatment and control arms relating to; i] URTI-related relapse rate. ii] Overall relapse rate (i.e. URTI related relapses plus non-URTI related relapses). iii] Cumulative dose of prednisolone received. iv] Proportion of subjects who develop, and severity of, steroid-related adverse events including behavioural problems. v] Proportion of subjects who undergo both escalation and reduction of immunosuppressive therapy. vi] Economic evaluation of cost per relapse and cost per QALY gained.
Exploratory Objectives	A single 10ml sample of blood will be collected for DNA and RNA extraction. This will be divided into two 5ml portions and used to i] Perform a genome wide association study to look for possible genetic loci associated with steroid sensitive nephrotic syndrome (in collaboration with Dr Detlef Bockenhauer and Professor Robert Kleta, Great Ormond Street Hospital and Institute of Child Health, University College, London) ii] Perform whole exome screening, initially looking for the 22 genetic mutations known to date to be associated with nephrotic syndrome, then moving to the 4000 genes expressed in the podocyte (key cell within the kidney filter) and finally to the entire exome. RNA will be used to perform functional studies to ascertain whether any detected mutation is pathogenic (in collaboration with Dr Ania Koziell and Professor Moin Saleem, Kings College London and University of Bristol)
Safety Monitoring	Adverse events will be assessed at each study visit.

	Important expected adverse events will be actively surveyed (i.e. must be assessed to complete the case report form). Serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) occurring over the 12 month study period and up to 3 months post treatment will be reported within 24 hours to the Birmingham Clinical Trials Unit (BCTU). An independent Data Monitoring and Ethics Committee (DMEC) will review adverse event data annually or more frequently if requested by the DMEC.

Study schema

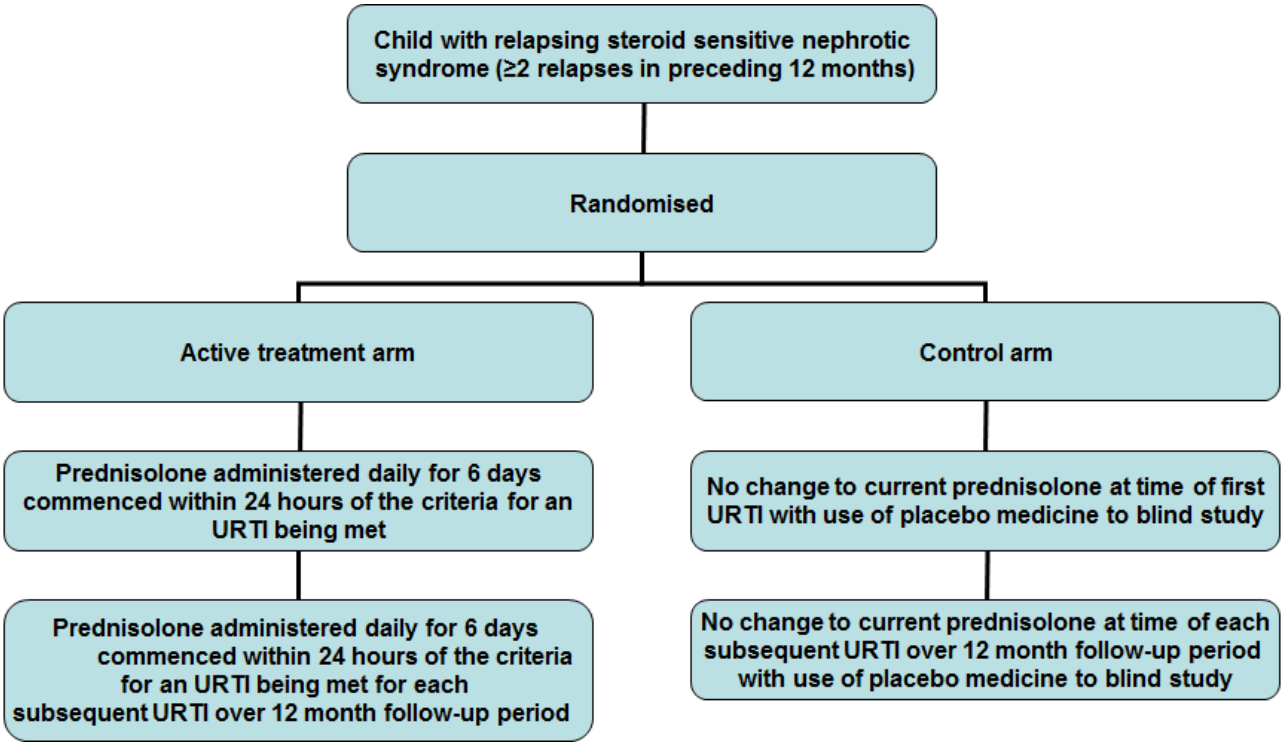


Table of Abbreviations

A+E	Accident and Emergency
ACBC	Achenbach Child Behaviour Checklist
AE	Adverse event
AR	Adverse reaction
BCH	Birmingham Children's Hospital
BCTU	Birmingham Clinical Trials Unit (also known as the Study Office)
BNF	British National Formulary
BSA	Body surface area
CHU-9D	Child Health Utility 9D
CI	Confidence interval
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trial Authorisation
DMEC	Data Monitoring and Ethics Committee
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
HTA	Health Technology Assessment
ICH-GCP	International Conference on Harmonisation Guidelines for Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISKDC	International Study of Kidney Disease in Children
MCD	Minimal change disease
MHRA	Medicines and Healthcare products Regulatory Agency
MMF	Mycophenolate mofetil
NeST	Nephrotic Syndrome Trust
NIHR	National Institute for Health Research
NS	Nephrotic syndrome
Parent	Parent or guardian of the study participant
PSSRU	National Schedule for Reference Costs and the Unit Costs of Health and Social Care
QALY	Quality Added Life Years
R+D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RNA	Ribonucleic acid
SAE	Serious Adverse Event

SAR	Serious adverse reaction
SD	Standard deviation
SmPC	Summary of Product Characteristics
SSNS	Steroid sensitive nephrotic syndrome
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Group
URTI	Upper respiratory tract infection

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1.SUMMARY

Minimal change nephrotic syndrome is the commonest glomerular disease of childhood [Trompeter et al, 1985]. The presenting episode is treated with high dose oral prednisolone to which >90% make a complete response, responders receiving the diagnostic label of steroid sensitive nephrotic syndrome (SSNS) [Trompeter et al, 1985]. The optimum duration of prednisolone therapy at presentation remains unclear and is currently being investigated in the PREDNOS study (HTA 08/53/31).

Following successful initial treatment, 70-80% of children develop disease relapses necessitating further courses of high dose prednisolone, and around 50% develop frequently relapsing disease [International Study of Kidney Disease in Children, 1982]. Long term low dose maintenance prednisolone is the most commonly prescribed therapy to reduce relapse frequency, though a number will require additional immunosuppressive agents including levamisole, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil (MMF) and rituximab.

Nephrotic syndrome relapses are associated with a risk of significant complications, including sepsis, thrombosis, dyslipidaemia and malnutrition [Webb, 2008]. The treatment of relapses with high dose prednisolone is associated with major adverse effects, including hip avascular necrosis, hypertension, diabetes and behavioural problems. Further, children are kept off school during relapses, resulting in impaired education performance and parental absence from work.

It is well recognised that at least 50% of relapses are precipitated by viral URTI, possibly mediated through release of cytokines [MacDonald et al, 1986]. 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.

Three studies published to date suggest that in children from developing countries (Saudi Arabia, Sri Lanka and India) with relapsing SSNS receiving long-term alternate day prednisolone therapy, the use of a short course of daily prednisolone therapy at the time of intercurrent URTI associated with fever 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) [Mattoo et al, 2000, Abeyagunawardena et al, 2008, Gulati et al, 2011]. These studies had a number of methodological problems, and have not identified:

1. Whether this is the case in children from developed countries, where the pattern of childhood URTI is significantly different (lower incidence of fever, absence of diarrhoea etc.);
2. Whether this effect occurs in children receiving long term maintenance prednisolone therapy in conjunction with other immunosuppressive therapies e.g. levamisole, ciclosporin, tacrolimus and MMF;
3. Whether this effect occurs in children receiving levamisole, ciclosporin, tacrolimus, and MMF without long term maintenance prednisolone therapy;
4. Whether this effect occurs in children on no long-term immunosuppressive therapy;
5. Whether there is an increase in the incidence of prednisolone-related adverse effects, including behavioural abnormality associated with the use of this intervention;
6. The cost-effectiveness analysis of such an approach, using a decision-analytic modelling approach.

The PREDNOS 2 study will provide important definitive evidence to address these outstanding questions. In this study, a total of 360 children will be randomised to receive either a six day course of daily prednisolone or no change to their ongoing immunosuppressive therapy (with the use of placebo to double blind the study) each time they develop an URTI over a 12 month period. The primary end point of the study will be the development of an URTI-related relapse after an URTI suffered during the 12 month follow-up study period. Close attention will be paid to the development of adverse effects of prednisolone therapy, including cosmetic and behavioural changes. The study will also collect detailed information on quality of life and health outcomes to allow a comprehensive health economic analysis to be performed. A single 10ml blood sample will be collected from study participants for the isolation of DNA and RNA. Using genome wide association study and total exome sequencing methodologies, we will search for potential candidate genes for SSNS and also identify potential candidate genes which might influence response to steroid therapy and the development of adverse effects.

2. GENERAL INFORMATION

2.1 Study Co-sponsors

Central Manchester University Hospitals NHS Foundation Trust
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Manchester Royal Infirmary
Oxford Road
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And

The University of Birmingham
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B15 2TT
United Kingdom

2.2 Ethical approval

The study has been approved by the North West GM Central Research Ethics Committee Ref: 12/NW/0766

2.3 EudraCT number

2012-003476-39

2.4 MHRA Clinical Trials Authorisation

21761/0281/001-0001

2.5 Clinical Research Network

The study has been adopted by the NIHR Clinical Research Network: Children.

2.6 Chief Investigator

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2.7 Co-Investigators

University of Birmingham	**NIHR Medicines for Children Research Network Nephrology Clinical Studies Group**
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Mrs Elizabeth Brettell	Prof Moin Saleem (Bristol)
	Dr Martin Christian (Nottingham)
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	Dr Ania Koziell (London)
	Dr Heather Maxwell (Glasgow)
	Dr Shivram Hegde (Cardiff)
	Dr Eric Finlay (Leeds)
	Dr Rodney Gilbert (Southampton)
	Ms Jenny Booth (Newcastle)
	Dr Caroline Jones (Liverpool)
	Dr Karl McKeever (Belfast)
	Mrs Wendy Cook (consumer representative)

2.8 Name and address of trial co-ordinator and co-ordinating centre

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2.9 Trial Steering Committee

Membership of the Trial Steering Committee:

Independent Trial Steering Committee

Dr Megan Thomas (Independent Expert and Chair), Dr Nigel Coad (Independent Expert), Mrs Sandra Cope (Independent Consumer Representative), Dr Andrew Duncan (Independent Expert), Dr Darren Green (Independent Expert), Dr Zala Ibrahim (Independent Expert), Dr Ly-Mee Yu (Independent Expert Statistician)

Additional non-independent members of Trial Steering Committee

Miss Natalie Ives (BCTU Statistician), Professor Nicholas Webb (Chief Investigator).

Additional Trial Steering Committee Attendees (non-members)

Miss Emma Barsoum (BCTU Study Coordinator), Mrs Elizabeth Brettell (BCTU Renal Trials Manager), Dr Martin Christian (Principal Investigator), Professor Peter Clayton (External Expert), Mrs Wendy Cook (Consumer Representative), Dr Richard Coward (Investigator), Dr Carole Cummins (External Expert), Dr Emma Frew (Health Economist), Mr Adam Khan (BCTU Renal Data Manager), Mrs Charmaine Hunt (BCTU Renal Trial Administrator), Dr Richard Trompeter (External Expert), Miss Rebecca Wooley (Statistician).

2.10 Trial Management Committee

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2.11 Data Monitoring Committee

Membership of Data Monitoring Committee:

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2.12 Sponsor's medical expert for the trial

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2.13 Protocol and protocol amendments

Any changes will be authorised by the Chief Investigator, Prof Nicholas Webb and approved by the MHRA and Health Research Authority (HRA).

2.14 Services Involved

Birmingham Children's Hospital Pharmacy will dispense the study drugs centrally for this trial.

No other services are involved.

3.BACKGROUND

3.1 Study rationale / introduction

Minimal change nephrotic syndrome is the commonest glomerular disease of childhood [Trompeter et al, 1985]. The presenting episode is treated with high dose oral prednisolone to which >90% make a complete response, responders receiving the diagnostic label of steroid sensitive nephrotic syndrome (SSNS) [Trompeter et al, 1985]. The optimum duration of prednisolone therapy at presentation remains unclear and is currently being investigated in the PREDNOS study (HTA 08/53/31, Chief Investigator Prof Nicholas Webb).

Following successful initial treatment, 70-80% of children develop disease relapses necessitating further courses of high dose prednisolone, and around 50% develop frequently relapsing disease [International Study of Kidney Disease in Children, 1982]. Long term low dose maintenance prednisolone therapy is the most commonly prescribed therapy to reduce relapse frequency, though a number will require additional immunosuppressive agents including levamisole, cyclophosphamide, ciclosporin, tacrolimus and mycophenolate mofetil (MMF).

Nephrotic syndrome relapses are associated with a risk of significant complications, including sepsis, thrombosis, dyslipidaemia and malnutrition [Webb, 2008]. The treatment of relapses with high dose prednisolone is associated with major adverse effects, including hip avascular necrosis, hypertension, diabetes and behavioural problems. Further, children are kept off school during relapses, resulting in impaired education performance and parental absence from work.

It is well recognised that at least 50% of relapses are precipitated by viral URTI, possibly mediated through release of cytokines [MacDonald et al, 1986]. 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.

Summary of previous studies investigating the use of daily prednisolone therapy at the time of URTI

Current practice in the large majority of UK centres is for no change to be made to immunosuppressive therapy at the time of development of an URTI. Three previous studies have assessed whether the use of daily prednisolone at the time of URTI reduces the subsequent risk of relapse of nephrotic syndrome.

Mattoo *et al* studied 36 Saudi children with relapsing SSNS who were receiving a long-term maintenance dose of alternate day prednisolone 'of about 0.5mg/kg/day' [Mattoo et al, 2000]. Starting on the day of onset of URTI (defined by onset of cough and/or cold with or without fever) subjects were alternatively assigned in an unblinded manner to receive either 5 days of daily prednisolone or to remain on alternate day prednisolone. They were then followed for a total of 2 years. The number of disease relapses (defined as Albustix 3+ positivity on morning urinalysis for 3 days) was documented in each group. Patients who did not relapse and patients who did not achieve remission with cyclophosphamide were both excluded. In the 18 children assigned to daily prednisolone at the time of URTI, the rate of relapse was lower than in the 18 children who continued on alternate day prednisolone (relapse rate (mean ± standard deviation (SD)): 2.2 ± 0.87 vs. 5.5 ± 1.33, p=0.04). The intervention arm received a median of 7 courses of daily prednisolone over the 2 year follow-up period. No difference was noted in the frequency of hospitalisations or the length of treatment for relapses between the two treatment arms.

Abeyagunawardena *et al* recruited 48 Sri Lankan children into a randomised double-blind cross-over study [Abeyagunawardena et al, 2008]. All were receiving long-term low dose alternate day prednisolone (mean 0.36mg/kg; range: 0.1 to 0.6mg/kg). Subjects were studied over 2 consecutive URTIs (defined as cough, runny nose, sore throat, lethargy, body aches, fever with no evidence of bacterial infection) and randomised to receive either daily prednisolone for 7 days or to continue on alternate day prednisolone (with placebo being administered on non treatment days to maintain the blind). Those who received daily prednisolone for the first URTI received alternate day prednisolone plus placebo for the second URTI, and vice versa. Children were reviewed on days 3 and 7 to assess for evidence of disease relapse (defined as Albustix 3+ proteinuria for 3 consecutive days). Those who developed prednisolone related adverse events; those who relapsed frequently and were prescribed steroid sparing therapy; those in whom prednisolone was discontinued due to sustained remission; and those who did not have two viral infections were all excluded from the study (8 of 48 recruited, thus 40 children completed the trial). Overall, there were 7 (18%) relapses following 40 URTIs treated with daily prednisolone and 19 (48%) relapses following URTI where alternate day prednisolone and placebo were administered (p=0.014; 2-sided Fishers exact test). No significant adverse effects were encountered.

The most recent and largest study was performed in 100 Indian children recently diagnosed with frequently relapsing SSNS 'eligible for therapy with long-term alternate day prednisolone with or without levamisole' [Gulati et al, 2011]. Children were recruited in stable remission, having received alternate day prednisolone 1.5mg/kg for 4 weeks, and then tapered by 0.25mg/kg every 2 weeks, until a dose of 0.5-0.75mg/kg on alternate days was reached. If a dose of prednisolone greater than 1mg/kg on alternate days was required, then levamisole was added. Children were randomised (stratified according to whether they received levamisole (n=32) or not (n=68)) to either daily prednisolone for 7 days or to remain on alternate day prednisolone in an unblinded manner at the time of development of URTI (defined as fever >38^{o}C, rhinorrhoea or cough for >1 day and

diarrhoea for >2 days). Children were reviewed every 2 months for a total of 12 months. The primary endpoint was the incidence of infection-associated relapse, with secondary endpoints of infection frequency and type and cumulative dose of prednisolone. Patients exited the study if there were 2 or more relapses in any 6 month period. Daily prednisolone therapy at the time of URTI resulted in a reduction in the incidence of infection-associated relapse (0.7 vs. 1.4; rate difference: 0.7, 95% confidence interval (CI): 0.3 to 1.1; $p<0.01$) and the overall relapse rate (0.9 vs. 1.8; rate difference: 0.9, 95% CI: 0.4 to 1.4; $p<0.0001$). Whilst not powered to do so, a sub-analysis showed that this difference was lost in those receiving levamisole. Nineteen children in the daily prednisolone group vs. 7 in the alternate day group remained relapse-free over the entire 12 month study period ($p=0.03$). There was no difference in cumulative prednisolone dose between the two arms. More infections occurred in the daily prednisolone group (226 vs. 161; $p=0.04$), though no difference was detected in height SDS, Cushingoid features, cataract or serious infection. A total of 6 children (2 in daily steroid group) exited the study because of treatment failure necessitating treatment with cyclophosphamide or calcineurin inhibitors.

Critique of previous studies investigating the use of daily prednisolone therapy at the time of URTI and summary of findings

The first two studies were small, underpowered, and contained a number of methodological and analysis flaws [Mattoo et al, 2000; Abeyagunawardena et al, 2008]. Mattoo's patients were assigned to treatment group on an alternate basis, which could have introduced bias due to lack of allocation concealment. The use of a cross-over design in Abeyagunawardena's study may have resulted in the first treatment course influencing the second, required each patient to have two URTIs (which was not the case in 3 patients) and only studied patients over the course of two relapses. Mattoo's study made no mention of power calculations, and whilst Abeyagunawardena stated that the study was aiming to detect a 50% reduction in relapse rate, the sample size required to achieve this was not stated. Adverse event incidence reporting was also sparse. The Mattoo and Gulati studies were not placebo-controlled, and in the latter all patients recruited had early steroid dependent disease. In patients receiving alternate day levamisole in combination with alternate day prednisolone, there was no statistically significant benefit associated with the use of daily prednisolone during URTI, however the study was not powered to answer this question. Finally, all studies excluded patients from the analyses for a variety of reasons which could have introduced bias (e.g. patients who did not suffer any relapses, patients who discontinued prednisolone treatment due to sustained remission, patients who continued to suffer frequent relapses and were prescribed alternative immunosuppressive therapies).

In summary, the three studies published to date suggest that in children from developing countries with relapsing SSNS receiving long-term alternate day maintenance prednisolone therapy, the use of daily prednisolone therapy at the time of intercurrent URTI associated with fever 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). However, as outlined above, these studies had a number of methodological problems, and these studies have not identified:

i] Whether this is the case in children from developed countries, where the pattern of childhood URTI is significantly different (lower incidence of fever, absence of diarrhoea etc.);

ii] Whether this effect occurs in children receiving long term maintenance prednisolone therapy in conjunction with other immunosuppressive therapies e.g. levamisole, ciclosporin, tacrolimus and MMF;

iii] Whether this effect occurs in children receiving levamisole, ciclosporin, tacrolimus, and MMF without long term maintenance prednisolone therapy;

iv] Whether this effect occurs in children on no long-term immunosuppressive therapy;

v] v] Whether there is an increase in the incidence of prednisolone-related adverse effects, including behavioural abnormality associated with the use of this intervention;

vi The cost-effectiveness analysis of such an approach, using a decision-analytic modelling approach.

A meeting was convened in January 2012 to discuss this study to which the members of the NIHR Medicines for Children Research Network (MCRN) Nephrology Clinical Studies Group, representing each of the 13 tertiary paediatric nephrology centres in the UK were invited to attend. A number of consumer representatives, including the Chairperson of the UK Nephrotic Syndrome Trust (NeST) and other parents of children with nephrotic syndrome were also in attendance. It was clear from this meeting that interest not only lay in the two cohorts originally included in the expression of interest, but also in those receiving other immunosuppressant therapies (with or without prednisolone) for their nephrotic syndrome. A single pragmatic trial was designed to include all patients with relapsing SSNS, in order to answer the overarching question of whether treatment with a short course of daily prednisolone at the time of upper respiratory tract infection (URTI) in children with relapsing SSNS reduces the subsequent development of nephrotic syndrome relapse. The results of the study will therefore be widely generalisable.

If this study were to show that the administration of a short course of daily prednisolone at the time of URTI effectively and safely reduces the rate of disease relapse in UK children this would alter practice both in the UK and other developed nations. There are already a small number of centres who routinely increase prednisolone doses at the time of URTI in individual patients, but the large majority do not because of a lack of sound evidence upon which to base such practice. A reduction in the nephrotic syndrome relapse rate would reduce relapse- and treatment-associated morbidity and hospitalisation rates and reduce parental time absent from work.

3.2 Research question

Does a six day course of daily prednisolone given early in the course of URTI in children with relapsing SSNS effectively and safely reduce the incidence of subsequent URTI-related relapse?

3.3 Investigational medicinal product

Prednisolone is a licensed corticosteroid immunosuppressant. Subjects will receive a supply of 100 tablets of study drug; prednisolone or matching placebo tablets which are being used to blind the study. Both are produced by the same supplier.

3.4 Name of supplier

Essential Nutrition Ltd. Bank House, Saltgrounds Road, Brough HU15 1EG UK

3.5 Summary of known and potential risks and benefits

Please use section 4.8 of the Wockhardt UK Ltd dated 31st March 2008 SmPC for prednisolone tablets. Please see Appendix 2 for Prednisolone Expected Adverse Events.

IMPs will only be used for trial subjects.

3.6 Trial conduct

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

4. TRIAL DESIGN

4.1 Introduction

Design: PREDNOS 2 will be conducted as a phase III randomised parallel group, placebo-controlled, double-blind trial.

Population to be studied: Children with relapsing SSNS (≥2 relapses in preceding 12 months).

Active treatment arm: Prednisolone 15mg/m^2/day as a single morning dose for six days commenced within 24 hours of the criteria for an URTI being met.

Control arm: Placebo (identical number of tablets) as a single morning dose for six days commenced within 24 hours of the criteria for an URTI being met.

4.2 Inclusion criteria

Subjects aged over 1 year and less than 19 years will be eligible for inclusion if they have relapsing SSNS, defined as **having experienced 2 or more relapses in the preceding 12 months**. This will include the following groups:

- Subjects on no long-term immunosuppressive therapy;
- Subjects receiving long term maintenance prednisolone therapy at a dose of up to and including 15mg/m^2 on alternate days;
- Subjects receiving long term maintenance prednisolone therapy at a dose of up to and including 15mg/m^2 on alternate days in conjunction with other immunosuppressive therapies, including levamisole, ciclosporin, tacrolimus, MMF, mycophenolate sodium and azathioprine;
- Subjects receiving long-term immunosuppressive therapies, including levamisole, ciclosporin, tacrolimus, MMF, mycophenolate sodium and azathioprine without long term maintenance prednisolone therapy.
- Subjects who have previously received a course of oral or intravenous cyclophosphamide:
    - Must have experienced two relapses in the 12 months prior to randomisation (in keeping with all other subjects)
    - Must have experienced at least one of these relapses following completion of cyclophosphamide therapy
    - Must be at least 3 months post completion of oral or intravenous cyclophosphamide therapy.
- Subjects who have previously received a single dose or course of intravenous rituximab:

    - Must have experienced two relapses in the 12 months prior to randomisation (in keeping with all other subjects)
    - Must have experienced at least one of these relapses following completion of rituximab therapy
    - Must be at least 3 months post completion of intravenous rituximab therapy.
- Parents and (where age appropriate) subject understand the definition of URTI and the need to commence study drug once this definition has been met.
- Written informed consent obtained from the subject's parents/guardians and written assent obtained from subject (where age appropriate). Subjects aged 16 years and above will provide their own written informed consent.

It is expected that there will be relatively even representation of subjects across the four background therapy groups (no background immunosuppressive therapy, long term maintenance prednisolone therapy, long term maintenance prednisolone therapy plus other immunosuppressive therapies, other immunosuppressive therapies alone), but this will be monitored during the trial. There is no evidence to suggest that the incidence of URTI is different with any one treatment regimen compared with the others, or that the likelihood of URTI precipitating a relapse of nephrotic syndrome differs according to this background immunosuppressant therapy.

4.3 Exclusion criteria

- Subjects with steroid resistant nephrotic syndrome
- Subjects receiving, or within 3 months of completing a course of oral or intravenous cyclophosphamide
- Subjects receiving, or within 3 months of receiving a course of rituximab
- Subjects on daily prednisolone therapy at time of recruitment
- Subjects on a prednisolone dose of greater than 15mg/m^2 on alternate days at the time of recruitment*
- Subjects with a documented history of significant non-adherence with medical therapy
- Subjects who will be transferred from paediatric to adult services during the 12 month study period
- Subjects unable to take prednisolone tablets, even in crushed form.
- Known allergy to prednisolone

*This applies to dose of prednisolone at the time of randomisation only. If prednisolone dose increases during the 12 month study period e.g. after a relapse, subject may remain in the study.

4.4 Randomisation and allocation concealment

Following the informed consent process, which will be conducted in accordance with current GCP [Medical Research Council], and completion of the baseline assessments, subjects will be randomised at the level of the individual on a 1:1 basis to either the **active treatment** or **control** arm. Randomisation will be provided by a computer generated programme at the Birmingham Clinical Trials Unit (BCTU). The randomisation will be stratified by the treatment regimen that the subject is receiving at randomisation (no treatment; long term maintenance prednisolone therapy only; long term maintenance prednisolone therapy with other immunosuppressant therapy; other immunosuppressant

therapy only). Treatment allocation will only be revealed to the central pharmacy dispensing the study drug at Birmingham Children's Hospital.

Study drug will be manufactured, packed and labelled by Essential Nutrition. Following randomisation, subjects will be provided with a supply of 100 tablets (2 containers of 50 tablets) of study drug (prednisolone 5mg for those randomised to the **active treatment arm** or matching placebo for those randomised to the **control arm**). This will be sent directly to the family home from the central pharmacy at Birmingham Children's Hospital by Royal Mail registered post on a day convenient for the family. The study drug containers and their contents will appear identical in every way, thus maintaining the double-blind. Study drug labelling will comply with the applicable regulatory requirements and clinical trial specific labels will be attached to all treatment. Birmingham Children's Hospital Pharmacy will maintain drug accountability logs for dispensed and returned study drug according to their local policy. Central pharmacy at Birmingham Children's Hospital must document when contacted by the parent/patient to confirm receipt of IMP, as below.

Every subject participating in the study will also be issued with a standard pack containing:

i. Subject diary in which the results of the morning urinalysis, treatment administration and any consultations with healthcare professionals (GP, nurse, hospital A+E department etc.), development of URTI, commencement of study drug and details of medicines prescribed or purchased over the counter are to be recorded.
ii. Instructions on contacting the central pharmacy at Birmingham Children's Hospital on receipt of IMP at the family home. This will include date of receipt and number of bottles received.
iii. Electronic tympanometric thermometer to measure temperature at the time of suspected URTI (see below).
iv. Written and (if requested) electronically downloadable information regarding URTI definition.
v. Written and (if requested) electronically downloadable information regarding dose of study drug to be commenced in the event of URTI developing.
vi. Other 'aide memoirs' regarding definition of URTI etc. displayed on fridge magnets and laminated sheets.

4.5 Planned interventions

Current practice is for no change to be made to immunosuppressive therapy at the time of development of an URTI. The intervention being assessed within PREDNOS 2 is a 6 day course of daily prednisolone therapy at the time of onset of URTI.

Those randomised to the **active treatment arm** will commence on a 6 day course of daily prednisolone each time they develop an URTI (see below for strict definition) during the 12 month follow-up period. Those randomised to the **control arm** will receive an identical number of placebo tablets, thus allowing double blinding of the study. If the subject is receiving background long-term immunosuppressive therapy (e.g. levamisole, ciclosporin), then this should continue unchanged (see section 4.8).

4.6 Definition of an Upper Respiratory Tract Infection

An URTI will be defined as the presence of at least 2 of the following *for at least 24 hours*:

- sore throat
- ear pain/discharge
- runny nose
- cough (dry/barking)
- hoarse voice
- fever >37^{o}C (measured using tympanometric electronic thermometer)

Parents will be provided with clear written and (if requested) downloadable electronic information informing them of the study definition of an URTI as outlined above. They will also be provided with abbreviated versions of these printed onto laminated cards which can be kept in multiple locations within the family home including in fridge magnet format. An electronic tympanometric thermometer (Braun thermoscan) will be provided to the parents of all subjects to allow them to measure their child's temperature. A study diary will also be provided for parents to record the results of the daily morning urinalysis (standard of care in children with relapsing SSNS), development of URTI, commencement of study drug, other ongoing treatment, acute illnesses and other issues.

4.7 Commencement of study drug

Once the subject meets the definition for URTI (two or more criteria for at least 24 hours), the parents will commence their child on study drug (prednisolone 5mg tablets for those in the **active treatment arm** or placebo for those in the **control arm** according to randomisation). The precise dosing regimen will have been calculated at the baseline study visit at the time of their recruitment and will be reviewed at each study visit, or between study visits if there is a change in the dose of long term maintenance prednisolone therapy. Information about the precise number of study drug tablets to administer will be provided for the family in written form, using a standard form (Advice Letter to Parent/Patients) which will be completed by the investigator. Please ensure that a copy of the Advice Letter to Parent/Participants is copied and filed in the patient notes and site file. This information is considered as usual clinical information and as such should also be recorded in the patient notes. At each assessment please recalculate the study tablets needed if the patient develops a URTI, and as necessary if the subject's height, weight, surface area or background prednisolone therapy has changed. Please use the Dose Calculator on the online system and complete numbers in the Advice Letter to Parent/Participants. If a new Advice Letter to Parent/Participants is issued again please copy and file in the patient notes and site file and record the information in the patient notes.

It is anticipated that parents will have no difficulties in identifying that their child has met the URTI criteria and will be happy to commence study drug unassisted, having been provided with comprehensive advice at the time of their recruitment. However, to provide a secure back-up service in case of any doubt, parents will be instructed to contact their local study site, or in case this is not possible, a PREDNOS 2 study telephone number will be provided to the parents of all study subjects. This will be manned by the Chief Investigator or his nominated deputy during periods of annual leave etc. Parents will be able to seek advice regarding whether their child meets URTI criteria, the dose of study drug required, or any other issues relating to the study. A log of these telephone calls will be maintained, and the Chief Investigator will report their content to the local Principal Investigator by email.

To ensure patient safety, the information provided to parents will also contain information about signs of more serious infection (non-blanching rash, leg pain, cool extremities, rapid breathing, blue lips, fitting, unconsciousness or any other major concern). If any of these features are present, parents will be instructed not to start study drug and to seek urgent medical attention for their child from their GP or local Accident and Emergency Department.

Parents will be asked to contact their local study site before or within 24 hours of commencing study drug to inform the Principal Investigator or nominated deputy and to allow them the opportunity to discuss any of their child's symptoms that may be of concern to them. Please ensure, in accordance with GCP, that all contacts with parents/patients are recorded in the patient's medical notes, including telephone and email contacts. Paediatric centres regularly receive a significant number of telephone calls from the parents of children with SSNS as part of routine clinical care (e.g. for advice on the management of disease relapses, requests for information following exposure to infections etc.). Parents of children with SSNS all routinely perform regular and careful home-based monitoring of their child's condition, including daily urinalysis and monitoring for exposure to and development of infection. They are instructed to contact the paediatric centre when proteinuria recurs or whenever there are other concerns and thus the telephone call for the purpose of this study will represent a simple extension of this well established practice, but must be recorded in the medical notes.

This process should be repeated every time the child develops an URTI over the 12 month follow-up period. The only exception to this is if the child is receiving daily prednisolone therapy e.g. in the early stages of treatment for a previous relapse – in this instance study drug should not be commenced.

4.8 Dosing of study drug

The number of tablets of study drug (prednisolone 5mg for those in the **active treatment arm** and matching placebo for those in the **control arm**) to be administered once URTI develops will be calculated at the time of the baseline (randomisation) visit and will be reviewed at each subsequent visit, to allow any adjustment necessary because of changes in the child's body surface area or long term maintenance prednisolone dose.

1] Subjects not receiving long term maintenance prednisolone therapy at time of development of URTI

Subjects should receive a total number of study drug tablets equivalent to a prednisolone dose of 15mg/m^2 (maximum dose 40mg) for a total of 6 days given as 5mg tablets. Dosing should be rounded up or down to the nearest 5mg (maximum dose 40mg).

Example 1: a subject with a body surface area of 1.0 m^2.

Note: Body surface area is frequently used for drug dosing in paediatric practice and is most simply calculated using the Mosteller formula BSA=√(height.weight/3600) [Mosteller, 1987].

Prednisolone dose = 15mg daily for 6 days = 3 x 5mg tablets daily for 6 days

Subject should therefore receive 3 tablets of study drug (prednisolone for those in the **active treatment arm** or placebo for those in the **control arm**) for 6 days

Example 2: A subject with a body surface area of 1.2m^2

Prednisolone dose = 18mg daily for 6 days, rounded up to 20mg daily for 6 days = 4 x 5mg tablets daily for 6 days

Subject should therefore receive 4 tablets of study drug (prednisolone for those in the **active treatment arm** or placebo for those in the **control arm**) for 6 days

Example 3: A subject with a body surface area of 0.8m^2

Prednisolone dose = 12mg daily for 6 days, rounded down to 10mg daily for 6 days = 2 x 5mg tablets daily for 6 days

Subject should therefore receive 2 tablets of study drug (prednisolone for those in the **active treatment arm** or placebo for those in the **control arm**) for 6 days

Study drug should always be given as a single dose in the morning.

Co-administration of other immunosuppressive and other medications

If the subject is receiving an additional immunosuppressive therapy e.g. ciclosporin, levamisole etc., this should continue unchanged throughout the six day course of study drug. Other drug treatment should also continue unchanged.

At the end of the 6 day course of study drug, the subject should continue off all prednisolone therapy as previously. Other drug treatment should continue unchanged.

The study drug dose to be used on development of an URTI may change during the study due to alterations in the subject's long-term maintenance prednisolone dose and normal childhood growth. The precise regimen to be administered will be discussed with parents along with a written treatment plan at the time of recruitment and (in light of the above) will be re-discussed at each study visit. Where changes in long term maintenance prednisolone dose occur between study visits (e.g. as part of a planned reducing regimen), updated information will be sent to parents by mail or email. Parents will always have clear written instructions to inform them of the precise regimen of study drug to give to their child should they develop an URTI.

2] Children receiving long term maintenance prednisolone therapy at a dose of less than 15mg/m^2 on alternate days at time of development of URTI

Subjects should receive a total number of study drug tablets equivalent to a prednisolone dose of 15mg/m^2 (maximum dose 40mg) given as 5mg tablets. Dosing should be rounded up or down to the nearest 5mg (maximum dose 40mg).

Example 1: a subject with a body surface area of 1.0 m^2 receiving a long term maintenance prednisolone dose of 10mg (10mg/m^2) on alternate days

Note: Body surface area is frequently used for drug dosing in paediatric practice and is most simply calculated using the Mosteller formula BSA=√(height.weight/3600) [Mosteller, 1987].

At development of URTI, subject commences on study drug (5mg prednisolone or placebo) as follows so that the prednisolone dose received in the active treatment arm is 15mg/m^2 (equivalent to 15mg in this case) and those in the control arm receive an identical number of tablets, thus maintaining the double blind.

If day of commencement of study drug is a day when regular maintenance prednisolone is due,

Day 1 Prednisolone 10mg + 1 tablet of study drug
Day 2 3 tablets of study drug
Day 3 Prednisolone 10mg + 1 tablet of study drug
Day 4 3 tablets of study drug
Day 5 Prednisolone 10mg + 1 tablet of study drug
Day 6 3 tablets of study drug

If day of commencement of study drug is not a regular treatment day then,

Day 1 3 tablets of study drug
Day 2 Prednisolone 10mg + 1 tablet of study drug
Day 3 3 tablets of study drug
Day 4 Prednisolone 10mg + 1 tablet of study drug
Day 5 3 tablets of study drug
Day 6 Prednisolone 10mg + 1 tablet of study drug

This regimen will result in subjects randomised to the active treatment arm receiving prednisolone 15mg daily for 6 days and those randomised to the control arm undergoing no change in their therapy.

Example 2: A subject with a body surface area of 1.2m^2 receiving a long term maintenance prednisolone dose of 10mg (8.3mg/m^2) on alternate days

Note: Body surface area is frequently used for drug dosing in paediatric practice and is most simply calculated using the Mosteller formula BSA=√(height.weight/3600) [Mosteller, 1987].

At development of URTI, subject commences on study drug (5mg prednisolone or placebo) as follows so that the prednisolone dose received in the active treatment arm is 15mg/m^2 (equivalent to 20mg in this case – precise dose is 18mg, though rounded up to 20mg) and those in the control arm receive an identical number of tablets, thus maintaining the double blind.

If day of commencement of study drug is a day when regular maintenance prednisolone is due,

Day 1 Prednisolone 10mg + 2 tablets of study drug
Day 2 4 tablets of study drug
Day 3 Prednisolone 10mg + 2 tablets of study drug
Day 4 4 tablets of study drug
Day 5 Prednisolone 10mg + 2 tablets of study drug
Day 6 4 tablets of study drug

If day of commencement of study drug is not a regular treatment day then,

Day 1 4 tablets of study drug

Day 2 Prednisolone 10mg + 2 tablets of study drug

Day 3 4 tablets of study drug

Day 4 Prednisolone 10mg + 2 tablets of study drug

Day 5 4 tablets of study drug

Day 6 Prednisolone 10mg + 2 tablets of study drug

This regimen will result in subjects randomised to the active treatment arm receiving prednisolone 20mg daily for 6 days and those randomised to the control arm undergoing no change in their therapy.

Example 3: A subject with a body surface area of 0.8m^2 receiving a long term maintenance prednisolone dose of 10mg (12.5mg/m^2) on alternate days

Note: Body surface area is frequently used for drug dosing in paediatric practice and is most simply calculated using the Mosteller formula BSA=√(height.weight/3600) [Mosteller, 1987].

At development of URTI, subject commences on study drug (5mg prednisolone or placebo) as follows so that the prednisolone dose received in the active treatment arm is 15mg/m^2 (equivalent to 10mg in this case – precise dose is 12mg, though rounded down to 10mg) and those in the control arm receive an identical number of tablets, thus maintaining the double blind.

If day of commencement of study drug is a day when regular maintenance prednisolone is due,

Day 1 Prednisolone 10mg + 0 tablets of study drug

Day 2 2 tablets of study drug

Day 3 Prednisolone 10mg + 0 tablets of study drug

Day 4 2 tablets of study drug

Day 5 Prednisolone 10mg + 0 tablets of study drug

Day 6 2 tablets of study drug

If day of commencement of study drug is not a regular treatment day then,

Day 1 2 tablets of study drug

Day 2 Prednisolone 10mg + 0 tablets of study drug

Day 3 2 tablets of study drug

Day 4 Prednisolone 10mg + 0 tablets of study drug

Day 5 2 tablets of study drug

Day 6 Prednisolone 10mg + 0 tablets of study drug

This regimen will result in subjects randomised to the active treatment arm receiving prednisolone 10mg daily for 6 days and those randomised to the control arm undergoing no change in their therapy.

Study drug should always be given as a single dose in the morning.

Co-administration of other immunosuppressive and other medications

If the subject is receiving an additional immunosuppressive therapy e.g. ciclosporin, levamisole etc., this should continue unchanged throughout the six day course of study drug. Other drug treatment should also continue unchanged.

At the end of the 6 day course of study drug, the subject should continue on their previous dose of long term maintenance prednisolone therapy. Other drug treatment should continue unchanged.

The study drug dose to be used on development of an URTI may change during the study due to alterations in the subject's long-term maintenance prednisolone dose and normal childhood growth. The precise regimen to be administered will be discussed with parents along with a written treatment plan at the time of recruitment and (in light of the above) will be re-discussed at each study visit. Parents will always have clear written instructions to inform them of the precise regimen of study drug to give to their child should they develop an URTI.

3] Children receiving prednisolone therapy at a dose of greater than 15mg/m^2 on alternate days at the time of development of URTI

Note - this will represent the minority of study subjects, as one of the key exclusion criteria for randomisation is subjects receiving a prednisolone dose which is greater than 15mg/m^2 on alternate days. There will, however, be subjects who develop a disease relapse (either URTI related or non-URTI related) during the course of the 12 month study and may therefore be receiving a higher dose of prednisolone at the time of development of an URTI. This could be the first URTI, around which the primary end point of the study is based, or a subsequent URTI. The management should be the same in both instances and is as follows;

Subjects should receive a total number of study drug tablets equivalent to the alternate daily prednisolone dose being received (maximum dose 60mg) given as 5mg tablets. Dosing should be rounded up or down to the nearest 5mg (maximum dose 60mg).

Example 1: a subject with a body surface area of 1.0 m^2 receiving a prednisolone dose of 20mg (20mg/m^2) on alternate days

Note: Body surface area is frequently used for drug dosing in paediatric practice and is most simply calculated using the Mosteller formula BSA=√(height.weight/3600) [Mosteller, 1987].

At development of URTI, subject commences on study drug (5mg prednisolone or placebo) as follows so that the daily prednisolone dose received in the active treatment arm is equivalent to the current alternate daily dose - 20mg/m^2 (equivalent to 20mg in this case) and those in the control arm receive an identical number of tablets, thus maintaining the double blind.

If day of commencement of study drug is a day when regular maintenance prednisolone is due,

Day 1 Prednisolone 20mg + 0 tablets of study drug

Day 2 4 tablets of study drug

Day 3 Prednisolone 20mg + 0 tablets of study drug

Day 4 4 tablets of study drug

Day 5 Prednisolone 20mg + 0 tablets of study drug

Day 6 4 tablets of study drug

If day of commencement of study drug is not a regular treatment day then,

Day 1 4 tablets of study drug

Day 2 Prednisolone 20mg + 0 tablets of study drug

Day 3 4 tablets of study drug

Day 4 Prednisolone 20mg + 0 tablets of study drug

Day 5 4 tablets of study drug

Day 6 Prednisolone 20mg + 0 tablets of study drug

This regimen will result in subjects randomised to the active treatment arm receiving prednisolone 20mg daily for 6 days and those randomised to the control arm undergoing no change in their therapy.

Example 2: A subject with a body surface area of 1.2m^2 receiving a prednisolone dose of 25mg (20.8mg/m^2) on alternate days

Note: Body surface area is frequently used for drug dosing in paediatric practice and is most simply calculated using the Mosteller formula BSA=√(height.weight/3600) [Mosteller, 1987].

At development of URTI, subject commences on study drug (5mg prednisolone or placebo) as follows so that the daily prednisolone dose received in the active treatment arm is equivalent to the current alternate daily dose – 20.8mg/m^2 (equivalent to 25mg in this case) and those in the control arm receive an identical number of tablets, thus maintaining the double blind.

If day of commencement of study drug is a day when regular maintenance prednisolone is due,

Day 1 Prednisolone 25mg + 0 tablets of study drug

Day 2 5 tablets of study drug

Day 3 Prednisolone 25mg + 0 tablets of study drug

Day 4 5 tablets of study drug

Day 5 Prednisolone 25mg + 0 tablets of study drug

Day 6 5 tablets of study drug

If day of commencement of study drug is not a regular treatment day then,

Day 1 5 tablets of study drug

Day 2 Prednisolone 25mg + 0 tablets of study drug

Day 3 5 tablets of study drug
Day 4 Prednisolone 25mg + 0 tablets of study drug
Day 5 5 tablets of study drug
Day 6 Prednisolone 25mg + 0 tablets of study drug

This regimen will result in subjects randomised to the active treatment arm receiving prednisolone 25mg daily for 6 days and those randomised to the control arm undergoing no change in their therapy.

Study drug should always be given as a single dose in the morning.

Co-administration of other immunosuppressive and other medications

If the subject is receiving an additional immunosuppressive therapy e.g. ciclosporin, levamisole etc., this should continue unchanged throughout the six day course of study drug. Other drug treatment should also continue unchanged.

At the end of the 6 day course of study drug, the subject should continue on their previous dose of long term maintenance prednisolone therapy. Other drug treatment should continue unchanged.

The study drug dose to be used on development of an URTI may change during the study due to alterations in the subject's long-term maintenance prednisolone dose and normal childhood growth. The precise regimen to be administered will be discussed with parents along with a written treatment plan at the time of recruitment and (in light of the above) will be re-discussed at each study visit. Parents will always have clear written instructions to inform them of the precise regimen of study drug to give to their child should they develop an URTI.

4] Children receiving daily prednisolone at time of development of URTI

Where URTI occurs whilst children are receiving daily prednisolone e.g. in the early stages of treatment for a disease relapse, study drug should **not** be commenced. Subjects can continue to participate in the study and the subsequent URTI should be treated with study drug provided that they are receiving alternate day prednisolone by this point.

CLINICAL COURSE FOLLOWING STUDY DRUG TREATMENT AT TIME OF URTI; DEFINITION OF URTI-RELATED RELAPSE

Following commencement of study drug, parents will continue to monitor their child's urine in accordance with routine clinical care. **Where disease relapse occurs, the parents should contact their study centre in accordance with routine clinical care and treatment for disease relapse should be commenced.**

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

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

It is important that these definitions are adhered to for the purposes of the study, particularly for the first episode of URTI, which defines the primary end point of the study.

4.9 Treatment of relapse

Relapses should be treated in accordance with the ISKDC relapse regimen. Prednisolone should be commenced at a dose of 60mg/m^2 daily (maximum dose 80mg) until the urine has been negative or trace for three consecutive days, then reduced to 40mg/m^2 (maximum dose 60mg) on alternate days for four weeks (14 doses). A subsequent tapering dose can be used at the individual physician's discretion.

Where relapse therapy is commenced, long term maintenance prednisolone therapy (e.g. 10mg on alternate days) is discontinued. Where relapse occurs whilst the child is receiving the six day course of study drug, this should also be discontinued. Once the relapse regimen has been completed, long term maintenance prednisolone therapy may be recommenced at any dose at the PI's discretion.

Background immunosuppressive therapy other than prednisolone e.g. ciclosporin, mycophenolate mofetil, levamisole etc. should be continued unchanged throughout the relapse treatment period.

4.10 Escalation of background immunosuppressive therapy

Subjects will only undergo intensification of background immunosuppressive therapy (i.e. the addition of a new immunosuppressive agent) where there are two or more relapses of their nephrotic syndrome (URTI-related or unrelated) in any six month period or where there are unacceptable adverse effects of prednisolone or other therapy. These subjects will remain under follow-up, though intensification of immunosuppressive therapy is an important study secondary endpoint. Similarly immunosuppressive therapy will only be discontinued where there is freedom from relapse for at least six months or where there are unacceptable adverse effects of therapy.

4.11 The research setting

The study will be performed in approximately 100 paediatric centres throughout the UK using the network of sites that we have established for the PREDNOS study. This will include the 13 paediatric nephrology centres (Alder Hey Children's Hospital, Belfast Royal Children's Hospital, Birmingham Children's Hospital, Bristol Royal Hospital for Sick Children, Evelina Children's Hospital London, Royal Hospital for Sick Children Glasgow, Great North Children's Hospital Newcastle, Great Ormond Street Hospital London, Queens Medical Centre Nottingham, Royal Manchester Children's Hospital, St James's University Hospital Leeds, Southampton General Hospital, University Hospital of Wales Cardiff) and Leicester Royal Infirmary, where the Chief Investigator and study co-applicants are based.

4.12 Trial schema and study visit schedule

Please see Appendix 1 for trial schema

Visit	1	2	3	4	5
Month	0	3	6	9	12
Visit window		+/-2w	+/-2w	+/-2w	+/-2w
Inclusion/Exclusion criteria	x				
Informed Consent	x				
Randomisation	x				
Allocation of study number	x				
Documentation of URTI		x	x	x	x
Documentation of commencement of study drug		x	x	x	x
Documentation of recent relapse	x	x	x	x	x
Recent medical/drug history	x	x	x	x	x
Adverse event documentation		x	x	x	x
Compliance check (tablet count using counting triangle)***		x	x	x	x
Physical exam	x	x	x	x	x
Assessment of steroid toxicity	x	x	x	x	x
Height and weight	x	x	x	x	x
Blood pressure	x	x	x	x	x
Calculation of study drug dose to be administered in event of URTI and explanation / provision of documentation of this to parents – includes review of height, weight and BSA to confirm correct dose	x	x	x	x	x
If 3 or more courses of study drug have been administered since previous visit, confirm parental understanding of definition of URTI		x	x	x	x
Blood sample for DNA/RNA*	x*	x*	x*	x*	x*
Achenbach CBC**	x	x	x	x	x
Peds QL**	x	x	x	x	x
CHU-9D and EQ-5D**	x	x	x	x	x
Study drug returned to Birmingham Children's Hospital pharmacy for accountability					x

* Blood sample to be collected on one single occasion only. Sample required for all subjects (including those who previously participated in the PREDNOS study).

** See Appendix 4 for version to be used at different ages

*** tablet count details to be recorded in the medical notes and the CRF on each occasion

4.13 Recruitment

All children with relapsing SSNS will be under the care of a paediatric nephrologist and/or a general paediatrician, and will be reviewed at least once every 3 months in a hospital out-patient clinic. Potential subjects will be identified at the time of their routine clinic attendance. To facilitate recruitment, ethics approval will be sought for a letter and information on the trial to be mailed to the parents of potentially eligible children (and the child where age appropriate) 1 to 2 weeks prior to their appointment. This will allow time for the parent(s) and child to consider the information provided and discuss the study with their family and friends. At the clinic appointment, they will be approached by an appropriately trained member of the clinical team regarding entering the PREDNOS 2 study. This individual will discuss the trial with them in detail (informing them of any possible benefits or risks relating to participation) and also give them time to ask any questions that they may have regarding the trial. Informed consent will then be sought from the parent(s) and children (informed consent or assent according to age) who agree

to enter the study. The study has been adopted by the CRN for Children, and the Local Research Networks will assist with subject identification and the recruitment process.

4.14 Patient and carer information leaflet

The conduct of the trial will be in accordance with the Principles of Good Clinical Practice and applicable regulatory requirements.

For subjects under 16 years of age, the parent's written informed consent for their child to participate in the trial and the subject's assent as appropriate given the child's competence must be obtained before randomisation and after a full explanation has been given of the treatment options and the manner of treatment allocation.

Subjects of 16-18 years of age will give their own consent to participation in the study.

Information sheets for parents, subjects aged 16-18yrs, older children and younger children will be used where appropriate.

The subject's GP will be notified, with the parent's and/or subject's consent.

Sites will use the current, ethically approved version of the consent/assent forms, patient/parent information sheets and GP letter.

4.15 Informed Consent

It is the responsibility of the Investigator (or designate e.g. Research Nurse if local practice allows and this responsibility has been delegated by the Principal Investigator as captured on the Site Signature and Delegation Log) to obtain written informed consent for each parent/subject prior to performing any trial related procedure. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the parent/ subject. The Investigator should also stress that the subject is completely free to refuse to take part or withdraw from the trial at any time. The parent/subject should be given ample time (e.g. up to one week) to read the Parent/Patient Information Sheet and to discuss their participation with others outside of the site research team. The parent/subject must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the parent/ subject to refuse to participate in the trial without giving a reason must be respected.

If the parent expresses an interest in their child participating in the trial they should be asked to sign and date the current ethically approved version of the Informed Consent Form. The subject will sign their own consent form if aged 16-18 years inclusive or, if below 16 years may sign an assent form if age appropriate

The Investigator or designate must then sign and date the form. A copy of the Informed Consent/Assent Form should be given to the parent/subject, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the subject is entered into the trial the subject's trial number should be entered on the Informed Consent/Assent Form maintained in the ISF. In addition, a copy of the signed Informed Consent/Assent Form must be sent by fax to the Birmingham Children's Hospital Pharmacy Department. Details of the informed consent discussions should be recorded in

the subject's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Parent/Patient Information Sheet and Informed Consent Form. Throughout the trial the parent/ subject should have the opportunity to ask questions about the trial and any new information that may be relevant to the subject's continued participation should be shared with them in a timely manner.

Electronic copies of the Parent/Patient Information Sheet and Informed Consent/Assent Forms are available from the Study Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all subjects approached about the trial should be recorded on the Subject Screening/Enrolment Log and with the parent's/ subject's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

4.16 Randomisation

Subjects will be randomised online via a secure 24 hour internet based randomisation service, or by a telephone call to the BCTU once informed consent has been obtained. Randomisation will take place at the time of the initial study visit, prior to the development of the first URTI to ensure that study drug has reached the parents/subject by the time the first URTI develops. The Investigator must complete the Randomisation Notepad to prepare for, and be able to, randomise. The Randomisation Notepad must be signed by the investigator to indicate that all of the eligibility criteria have been checked. It should also be noted in the medical records that the investigator has checked all of the eligibility criteria and that the patient meets all of the inclusion criteria and none of the exclusion criteria. The signed Randomisation Notepad should be kept in the investigator site file and a copy sent to the Trials Office. Only delegated staff at the Birmingham Children's Hospital Pharmacy will be able to view the treatment allocation in order to dispatch the pots of study drug. This will be done via a secure login link to the randomisation programme once a subject has been randomised. This method of randomisation will ensure that investigators and the study office are blinded to the subject's treatment allocation to active treatment or placebo. Subjects will be randomised between the two treatment groups (active treatment or placebo) in a one-to-one ratio via the BCTU online randomisation service. This secure internet-based central randomisation service is available 24 hours a day and will ensure concealment of treatment allocation. The randomisation will be carried out by means of a minimisation algorithm, to ensure balance between the arms with regard to important covariates. The minimisation variables will be background therapy (no background immunosuppressive therapy, long term maintenance prednisolone therapy, long term maintenance prednisolone therapy plus other immunosuppressive therapies, other immunosuppressive therapies alone).

Informed consent must be obtained by the local investigator or other qualified local research staff, as detailed in Section 4.15, before randomisation is performed. The investigator should then log into the online randomisation service at https://www.trials.bham.ac.uk/PREDNOS2, which will ask the investigator to confirm the eligibility criteria. Eligible subjects will then be randomised to either active treatment or placebo. The subject will also be assigned a unique trial identification number to be used on all trial related material for the subject. Confirmation of the randomisation and trial identification number will be forwarded to the trial coordinator, the local investigator and the Birmingham Children's Hospital NHS Trust Pharmacy via e-mail immediately upon randomisation.

In the event that access to the internet is unavailable, the investigator may call the BCTU (0800 953 0274) during normal office hours (9am to 5pm GMT) who will access the randomisation program, randomise the subject and inform the investigator of the trial number and ensure that the randomisation information reaches the appropriate study personnel. The randomisation list will be produced using a block design with the program Sample Size 2.0.

Once the subject has been randomised and a PREDNOS 2 trial number has been obtained, the investigator must fax and send a signed copy of the Clinical Trial Prescription Form and the Consent/Assent Form(s) to the Pharmacy at Birmingham Children's Hospital, Fax: 0121 333 9776, , to order the PREDNOS 2 study drug.

4.17 Trial treatment

Prednisolone and placebo tablets will be manufactured by Essential Nutrition Ltd.

Subjects will be randomised to the active treatment or control arm. Subjects randomised to the active treatment arm will receive a supply of 100 prednisolone tablets for use at the time of development of URTI consistent with study intervention criteria. Subjects randomised to the control arm will receive an identically labelled supply of matching placebo tablets. For subjects unable to swallow the tablets whole, the prednisolone and placebo tablets can be crushed and a tablet crusher will be supplied with the study drug at the prescriber's request.

The pharmacy at Birmingham Children's Hospital NHS Trust will dispense and label the drugs and be responsible for drug accountability in line with their local policy. Study drug (2 containers of 50 tablets of prednisolone or placebo) will be contained within standard containers – these will be sent to study subject's home or an alternative address via Royal Mail Special Delivery following subject randomisation. Subjects will receive storage information with their study drug. If requested, study drug can be sent to the local investigator who is then responsible for ensuring the subject receives the study drug.

Compliance with study drug will be assessed at each study visit; this will be done by a manual pill count by the study nurse using a standard counting triangle.

4.18 Concomitant medications

All other medications are allowed as required through the trial. These should be recorded in the subject Case Report Forms (CRF).

4.19 Vaccination

Where the subject is due for routine vaccination, or specialised vaccinations, there are some contraindications which need to be taken into account as stated in the Department of Health's Immunisation Against Infectious Disease 1996, otherwise known as "The Green Book".

Live vaccines can, in some situations, cause severe or fatal infections in immunosuppressed individuals due to extensive replication of the vaccine strain. For this reason, severely immunosuppressed individuals should not be given live vaccines, and

vaccination in immunosuppressed individuals should only be conducted in consultation with an appropriate specialist. Inactivated vaccines cannot replicate and so may be administered to immunosuppressed individuals, although they may elicit a lower response than in immunocompetent individuals.

Subjects who receive prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2mg/kg/day for at least one week, or 1 mg/kg/day for one month are classified as a special risk group for being given live vaccines. Administration of live vaccines should be postponed for at least three months after immunosuppressive treatment has stopped, or three months after levels have been reached that are not associated with immunosuppression. Live vaccines include MMR and the BCG vaccine for tuberculosis. Also for parents who may wish to travel with their children other live vaccines include Yellow Fever and oral typhoid.

Where these issues arise with a subject within the trial please seek the advice of an immunologist or specialist within the field.

4.20 Follow-up assessments

All subjects will be followed-up for 12 months from randomisation, with subjects reviewed prior to randomisation and then once every three months for trial follow-up assessments (i.e. at 3, 6, 9 and 12 months post randomisation). This is entirely in keeping with the normal frequency of follow-up of this population in routine clinical practice. Follow-up assessments may be made by any appropriately qualified health professional included on the site delegation log. This may include study nurses or clinical nurse specialists as appropriate.

All parents and/or subjects will have previously been trained to perform early morning urine protein estimation as a part of routine clinical practice. They will be provided with a subject-held record book to enter the results of urine protein testing and the medication administered on a daily basis. This will be maintained for the 12 month duration of the study; monitoring of daily urinalysis forms part of routine care for this patient population. Parents will also use this diary to record any intercurrent illness and or consultations with healthcare professionals (GP, nurse, hospital A+E departments etc.), development of URTI and commencement of study medicines, along with details of medicines prescribed or purchased over the counter. Information from diaries reported by parents and subjects to consultants should be recorded in the medical records and on the study CRF. Please copy any patient diaries that are brought into clinic by the parent/participant and keep a copy in the patient notes and the site file. If the patient diaries are not returned to clinic, please record this in the patient notes. If the patient diaries are returned to clinic but are blank, please also record this in the patient notes.

4.21 Study visits

At the baseline visit:

- Confirmation of inclusion and exclusion criteria
- Informed consent/assent
- Randomisation and allocation of study number
- Information will be captured on dates of last two relapses
- Medical and drug history since diagnosis of nephrotic syndrome

- A physical examination will be performed, including measurement of height, weight and blood pressure
- Calculation of dose of study drug to be administered when URTI occurs and provision of written information for parents regarding this
- Scoring of prednisolone adverse effects will be performed by use of a standardised proforma
- In order to evaluate changes in subject behaviour associated with the different prednisolone regimens, the Achenbach Child Behaviour Checklist (ACBC) will be used. The ACBC is a standardised measure made up of 120 items measuring internalising (withdrawn, somatic complaints, anxiety/depression, thought problems) and externalising (social problems, attention problems, delinquent and aggressive) behaviour problems. A total Behavioural Problem score is calculated from these problem scales and forms the basis of comparison with age and gender-matched normative data.
- Information relating to quality of life will also be collected using the Child Health Utility (CHU)-9D and EQ-5D (dependent upon subject age) and PedsQL questionnaires.

At subsequent study visits (months 3, 6, 9 and 12):

- Details will be collected about any URTI that has developed and whether study drug has been commenced.
- Information will be captured regarding recent history of relapse and any treatment received for this.
- Recent other medical / drug history will be recorded.
- Adverse events will be documented.
- A study drug compliance check will be performed (tablet count using counting triangle).
- A physical examination will be performed, including measurement of height, weight and blood pressure.
- Scoring of prednisolone adverse effects will be performed by use of a standardised proforma.
- Recalculation of dose of study drug to be administered when URTI occurs and provision of written information for parents regarding this.
- If 3 or more courses of study drug have been administered since previous visit, confirmation of parental understanding of definition of URTI.
- Information will be collected about consultations with health care professionals in primary care (including the home) and also in hospital (both outpatient and inpatient) and any treatment administered;
- A record will be made of all medicines taken, including those prescribed and those purchased over the counter;
- Repeat administration of the Achenbach, CHU-9D and EQ-5D (dependent upon subject age) and PedsQL will be performed
- A blood sample for DNA and RNA analysis will be collected at one single visit.
- At the final (12 month) study visit, any remaining study drug will be returned to the Birmingham Children's Hospital Pharmacy for accountability.

4.22 Data Collection

The CRF will comprise of the following forms:

Form	Summary of data recorded	Schedule for submission
Randomisation Notepad	Subject details, confirmation of eligibility and clinical details.	Details collected via online randomisation and copy sent to BCTU following randomisation.
Baseline and follow-up CRFs	Clinical details, primary care visits, hospital admissions, hospital A&E visits, hospital outpatient visits, study drug, adverse effects, subject withdrawal.	Details collected via online data entry system at each follow-up assessment time point (baseline and months 3, 6, 9 and 12)
Serious Adverse Event (SAE) Form	Details of any SAE occurring over the 12 month study period and up to 3 months post treatment	Faxed/emailed within 24 hours of research staff becoming aware of event.
CHU -9D	Child Quality of Life (parent rated)	Details collected via online data entry systemafter follow-up assessment at month 0, 3, 6, 9 and 12.
EQ-5D	Child Quality of Life (parent rated)	Details collected via online data entry systemafter follow-up assessment at month 0, 3, 6, 9 and 12.
PedsQL	Child Quality of Life (parent rated)	Details collected via online data entry systemafter follow-up assessment at month 0, 3, 6, 9 and 12.
Achenbach (ACBC)	Child behaviour (parent rated)	Sent to BCTU after follow-up assessment month 0, 3, 6, 9 and 12.

Data from all CRF documents, except for the Achenbach Child Behaviour Checklist and SAE form, should be entered online directly by site staff at http://www.bctu.bham.ac.uk/PREDNOS2. To access the online data entry system, authorised staff at sites will be provided with an individual secure login username and be requested to set-up a password. Completed copies of the Achenbach Child Behaviour Checklist and SAE form should be forwarded to the PREDNOS 2 Trial Office for data entry. For details regarding the return of completed SAE forms, please see section 5.4 of the protocol.

Data reported on each eCRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the eCRF. All missing and ambiguous data will be queried. All sections are to be completed before returning.

Any information received from any source (parent/patient contact, patient diaries etc.) regarding development of URTIs and related symptoms, relapse dates and treatment, commencement of study medication, commencement or change of any medication especially prednisolone and other immunosuppressive therapies, must be documented in the patient notes.

All missing and ambiguous data will be queried via Data Clarification Forms (DCFs). Responses should be made on the DCF. The original DCF should be kept in the site file, and a copy of the DCF should be returned to the PREDNOS 2 Trial Office.

In all cases it remains the responsibility of the Investigator to ensure that the eCRF has been completed correctly and that the data are accurate.

Trial forms may be amended by the Study Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

4.23 Outcome Measures

4.23.1 Primary study endpoint:

First URTI-related relapse of nephrotic syndrome during 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. URTI-related relapse is defined as a relapse occurring within 14 days of the development of an URTI.

4.23.2 Secondary endpoints/ outcome measures:

Rate of URTI-related relapse of nephrotic syndrome (relapses per year)

Rate of relapse (URTI-related and non URTI-related) of nephrotic syndrome (relapses per year)

Cumulative dose of prednisolone (mg/kg and mg/m^2) received over the 12 month study period

Incidence of SAEs

Incidence of adverse effects of prednisolone including assessment of behaviour using the Achenbach Child Behaviour Checklist

Incidence of escalation of background immunosuppressive therapy (e.g. addition of ciclosporin, tacrolimus, cyclophosphamide etc.)

Incidence of reduction of background immunosuppressive therapy (i.e. cessation of long term maintenance prednisolone therapy)

Quality of life using the CHU-9D, EQ-5D and PedsQL

Cost per relapse of nephrotic syndrome

Cost per QALY gained

4.24 Monitoring of prednisolone related adverse effects

We will carefully monitor study subjects for prednisolone related adverse effects (see Appendix 2). As this is a Clinical Trial of an Investigational Medicine Product, we in any case need to document all adverse health events, their treatments and outcomes. Additionally to ensure that all adverse effects are recorded we will measure the following:

i. Height will be carefully monitored at each study visit (with the exception of telephone or home study visits) using a calibrated stadiometer with the subject in bare or stocking feet.
ii. Weight will be assessed at each study visit using calibrated scales.
iii. Body mass index standard deviation score will be calculated from i] and ii].
iv. Cushingoid features and hypertrichosis will be assessed by the clinician on a Likert scale and appetite will be assessed by the parent on a Likert scale.
v. The presence or absence of striae will be documented at each study visit.
vi. Behaviour will be assessed using the Achenbach Child Behaviour Checklist.
vii. Blood pressure will be assessed at each study visit to document the incidence of hypertension.
viii. Dipstick analysis of the urine will be performed at each study visit to look for glycosuria ***(>5mmol/l)***; where this is significant and persistent, plasma glucose will be measured in keeping with routine clinical practice.
ix. The development of significant bacterial, viral and fungal infections will be documented.
x. Use of varicella prophylaxis (zoster immune globulin or antiviral therapy) will be recorded.
xi. We will prospectively collect information regarding all episodes of consultation with General Practitioners or hospital medical teams, including data on treatments prescribed or purchased. This will be incorporated into the costs measured as part of the health economic analysis.

If any of the above prednisolone related adverse-effects meet the criteria of an SAE the event must be recorded on the SAE form and faxed to the BCTU on 0121 415 9135 within 24 hours of the research staff becoming aware of the event. Please try to ensure that the local Principal Investigator has assigned causality to the SAE before reporting.

4.25 Emergency unblinding

There may be medical emergencies where it is necessary for a subject's treatment to be unblinded. Unblinding should only occur when there are valid medical or safety reasons. Subject always to clinical need, where possible, members of the research team will remain blinded.

A code-break will be available via the BCH Pharmacy (see Unblinding Procedure: Appendix 3).

4.26 Withdrawal

Patients who cease study drug (i.e. those who do not want to start study drug at time of URTI) will be followed up for the entire duration of the study provided that consent for their ongoing participation in the study is not withdrawn.

Where consent is withdrawn, parents and subjects may choose any of the following;

- The subject may wish to withdraw from the investigational treatment, but is willing to be followed-up according to the trial protocol (i.e. has agreed that follow-up data can be collected and used in the final analysis)
- The subject may not want to attend trial specific follow-up visits but is willing to be followed-up according to standard practice (i.e. has agreed that follow-up data can be collected at standard clinic visits and used in the trial final analysis)

- The subject is not willing to be followed up for trial purposes at any further visits (but has agreed that any data collected prior to the withdrawal of consent can be used in the trial final analysis).

4.27 Blood sample collection for DNA isolation and sub studies

There are multiple reasons to suggest that SSNS may be a genetic disorder. As part of the PREDNOS 2 study, we will obtain DNA and RNA samples to identify changes w'hich may be the cause of or contribute to the disease process of SSNS. The discovery of genetic changes which are unique to SSNS would increase our understanding of the disease and may lead to improved, more specific therapies becoming available.

4.27.1 Blood sampling

As part of the consent process, permission will be obtained to collect a single 10ml blood sample for genetic sub studies at some point during the first year of follow-up, preferably at the time of routine venepuncture for clinical purposes. If for any reason the parents and or subject are unwilling to provide a blood sample, this will not preclude them taking part in the main study.

The 10ml blood sample will be collected into two 5ml aliquots standard blood sample tubes containing Potassium EDTA. Using pre-prepared stamped addressed packages designed to provide a safe transport system for biological, substances compliant with UK guidelines, both samples will be posted to Dr Bockenhauer and Professor Kleta's laboratory at the Institute of Child Health, London. One of the 5ml samples will be retained there and the other collected by a member of Dr Koziell's laboratory team from Guy's Hospital, London, to where it will be transferred.

Samples will be labelled with the subject's PREDNOS 2 study number and their date of birth in mmm/yyyy format only– there will be no personal information about the subject identifiable to the bench researchers.

Subjects will be asked whether they also agree to submit their DNA for future studies to help understand genetic links to related medical conditions, but will be equally free to opt out at any point in time and not do so. In this case a subject will be able to request and be assured that their particular sample has been destroyed after analysis for the PREDNOS 2 lab sub study.

4.27.2 Genome-wide association study of steroid sensitive nephrotic syndrome

This sub study will be performed in the laboratories of Professor Robert Kleta and Dr Detlef Bockenhauer at the Institute of Child Health, Great Ormond Street and the Royal Free Hospital, London (both laboratories are part of University College, London). The aim of the study is to identify any genetic mutations which may be associated with childhood SSNS. The identification of a genetic mutation associated with the development of SSNS would improve the understanding of the underlying disease mechanisms and might lead to future more specific therapies. Using DNA samples collected from study participants, a genome-wide association study will be performed utilizing up to date SNP chip technology and analysis. Identified risk alleles will undergo next generation sequencing to prove sequence variations within these alleles.

A separate application for funding for this work is currently being submitted.

4.27.3 Other genetic studies

This sub study investigating DNA mutations that might be important in the pathogenesis of relapsing SSNS will be conducted in collaboration with Dr Ania Koziell at Guy's Hospital, Kings College London and Professor Moin Saleem at the University of Bristol. The approach used will be whole exome screening. This represents a cost effective approach to identify the mutations of highest biomedical importance, generating information that can be used to help understand disease mechanisms and thus help improve treatment. As a consequence, exome screening has rapidly gained popularity in disease studies and has helped reveal many highly interesting causal loci not detectable by other methods. Initial data from whole genome sequencing has indicated that much of the diversity in the human genome is in rare DNA variants within the protein coding region or exome. These variants may cause or predispose to disease, with or without the need for an environmental trigger or modify response to treatment giving an explanation why different individuals respond to drugs in different ways. Eventually, the knowledge gained could help tailor drugs to particular individuals to get maximum response with minimum side-effects.

Preliminary data indicates that rare variants may also have a significant biological effect in childhood nephrotic syndrome, supporting their role in genetic susceptibility and progression of this disease, and possibly response to medication. Whole exome screening is the method of choice as it is more likely to provide information about genetic contribution than identifying common variants in regulatory regions; these are difficult to interpret in orphan diseases such as nephrotic syndrome with an incidence of less than 1 per 2000. Analysis of results will first examine a panel of 22 genes known to be associated with nephrotic syndrome, namely *WT1*, *NPHS1*, *NPHS2*, *CD2AP*, *LAMB2*, *LMX1B*, *TRCP6*, *INF2*, *ACTN4*, *PLCe1, RHGAP24*, *cubulin*, *MYO1E*, *COQ2, SCARB2, MHY9, APOL1, PDSS2, SMARCL1, PMM2, COL4A3, COL4A4* as these are cloned primarily through studies of families with autosomal recessive or dominant nephrotic disease, and less commonly pathogenic in the wider nephrotic population. If these test negative, bioinformatics analysis will examine the 4000 functional genes expressed in the podocyte. If no conclusive results are obtained, the remaining exome will undergo analysis. All analysis will be performed with appropriate bioinformatics support and subjected to rigorous statistical testing. Public databases of the human genome such as dBSNP and 1000genomes will be used as controls and standard mutation analysis programmes such as SIFT used to determine the functional significance of mutations.

RNA will also be isolated from the same 5ml blood sample. This will be used to perform functional studies to ascertain whether or not any identified mutation is pathogenic.

4.28 Sample Size

A total of 360 subjects will be recruited into the study (180 in each study arm).

The primary analysis will be based on a comparison of the number of **first** URTI-related relapses of nephrotic syndrome in the two study arms during the 12 month follow-up period. In children with frequently relapsing SSNS, the development of an URTI results in relapse in around 50% of instances [Abeyagunawardena et al, 2008]. In the Abeyagunawardena study, overall 40 URTIs treated with placebo were followed by 19 (48%) relapses, compared with 7 (18%) relapses in the prednisolone-treated group. This corresponds to an absolute difference of 30% (a 62.5% proportional reduction). In the first

treatment period, there were 10 (45%) relapses in 22 placebo-treated children compared with 4 (22%) relapses in 18 prednisolone-treated children (23% absolute difference, 51% proportional reduction) [Abeyagunawardena et al, 2008]. This is a large treatment effect based on a small study of children on long term maintenance alternate day prednisolone therapy in a developing country. Therefore to detect a more conservative difference of 17.5% (i.e. 35% proportional reduction) in URTI-related relapse rate (i.e. from 50% to 32.5%), with 80% power, 2-sided test and alpha=0.05, requires 250 subjects in total (comparison of two proportions [Machin et al]). If we allow 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), then this will require recruitment 360 subjects. We therefore propose to recruit 360 subjects, 180 to each arm. However, if the treatment effect is more in line with the 50% reduction observed in the first treatment period of the Abeyagunawardena study, then this study has sufficient power (>95%) to detect this difference. To detect a 50% proportional reduction (i.e. 50% to 25%) with 90% power and alpha=0.05, requires 154 subjects, increasing to 220 with allowance for 30% drop-out.

4.29 Statistical Analysis

The Statistical Analysis Plan describes the planned analyses for PREDNOS 2 in full detail. A summary of the main analysis methods are described here.

The primary endpoint is the first URTI-related relapse of nephrotic syndrome (URTI-related relapse is defined as 3 days of Albustix 3+ proteinuria within 14 days of onset of an URTI) which occurs during the 12 month follow-up period. The proportion of subjects that experience an URTI-related relapse will be calculated for the two study treatment arms, and compared using a chi-squared test. Treatment effects will be expressed as relative risks with 95% confidence intervals.

This was chosen as the primary endpoint as it is hypothesised that giving daily prednisolone at time of URTI will reduce the subsequent development of disease relapse. If this hypothesis is correct, then those subjects randomised to placebo will experience more URTI-related relapses than those subjects randomised to active drug. This would mean that subjects in the placebo arm are more likely to undergo intensification of immunosuppressive therapy. This in turn would reduce the chances of the subjects in the placebo arm from having further relapses (both URTI-related and non URTI-related) which introduces bias. Therefore, all subjects will be followed-up for 12 months to also assess the relapse rates between the two treatment arms over a 12 month period as a secondary endpoint, but due to these potential biases, the primary endpoint will focus on the first URTI-related relapse. The analysis of the secondary endpoints for relapses per year will assess incidence (relapse) density rates for the two treatment arms and rate differences will be calculated for both URTI- and non-URTI related relapse of nephrotic syndrome over the 12 month follow-up period. Appropriate regression analysis (e.g. Poisson) will be used to compare relapse rates in the two treatment groups, should there be an imbalance in any important co-variates (e.g. URTI rates across the two study arms).

The secondary endpoints include both continuous and categorical data items. The dichotomous data (e.g. incidence of escalation of background immunosuppressive therapy) will be analysed as per the primary outcome. Continuous data (e.g. prednisolone dose, quality of life scores) will be expressed as means and standard deviations, with differences in means and 95% confidence intervals. Longitudinal plots of the data over time will be constructed for visual presentation of the data. Data will be analysed using

mixed effect repeated measures models with the interventions specified as independent variables. Baseline data will be included in the model as a covariate.

Analyses will be of all randomised subjects using intention to treat, except for those who do not have an URTI following randomisation. Over the course of the study up to the 12th July 2016, the number of patients who have completed the trial without experiencing at least one URTI is approximately 24% which is higher than the originally estimated <10% at the start of the trial. Exclusion of these subjects will result in no bias as these drop-outs are not related to the treatment and should by chance be equally distributed across the two treatment arms (this will be monitored throughout the trial). Sensitivity analyses will be performed on the 12 month data analyses due to the issues raised above. These analyses will be fully outlined in the Statistical Analysis Plan, and will include analyses with subjects censored at point of treatment escalation.

The only subgroup analyses planned are by the background treatment regimen that the subjects are on at randomisation (no long-term treatment; on long term maintenance prednisolone therapy; on other immunosuppressant therapy with long term maintenance prednisolone therapy; on other immunosuppressant therapy without prednisolone); an analysis comparing those subjects on prednisolone versus those not on prednisolone; and an analysis comparing those subjects on other immunosuppressant therapy versus those not on other immunosuppressant therapy. The study is not powered to detect differences in treatment effect across these subgroups, so these analyses will be considered as hypothesis generating.

4.30 Health Economic analysis

The economic evaluation will involve the development of a decision analytic simulation model as a framework for conducting cost-effectiveness analysis. The modelling framework will allow additional exploration of scenarios that are not being specifically investigated as part of the primary study such as changing medication at different time points through the duration of the study (based on an assumption that the efficacy would remain unchanged). A modelling framework is ideally suited to demonstrate and explore these issues whilst accounting for any inherent uncertainty.

The economic evaluation will take the form of a cost-effectiveness analysis based on a primary clinical outcome of cost per episode of URTI-related relapse of proteinuria. Utility-based outcomes will also be incorporated into the model allowing a secondary outcome to be cost per quality-adjusted life year (QALY) gained (based on CHU-9D and EQ-5D values). Four different groups of subjects will be considered in the model: (i) subjects on no long-term immunosuppressive therapy; (ii) subjects receiving long term maintenance prednisolone therapy; (iii) subjects receiving long term maintenance prednisolone therapy in conjunction with other immunosuppressive therapies; and (iv) subjects receiving long-term immunosuppressive therapies without long term maintenance prednisolone therapy. For each of these four groups, the model will make a direct comparison between two strategies implemented each time a subject develops a URTI: the strategy of administering a course of daily prednisolone for 6 days and a strategy of no change to ongoing therapy (with the use of placebo tablets to maintain blinding). The base case economic evaluation will adopt the NHS perspective. NHS costs will include:

A. Treatment costs: medicines, management, adverse-effects, and treatment complications;

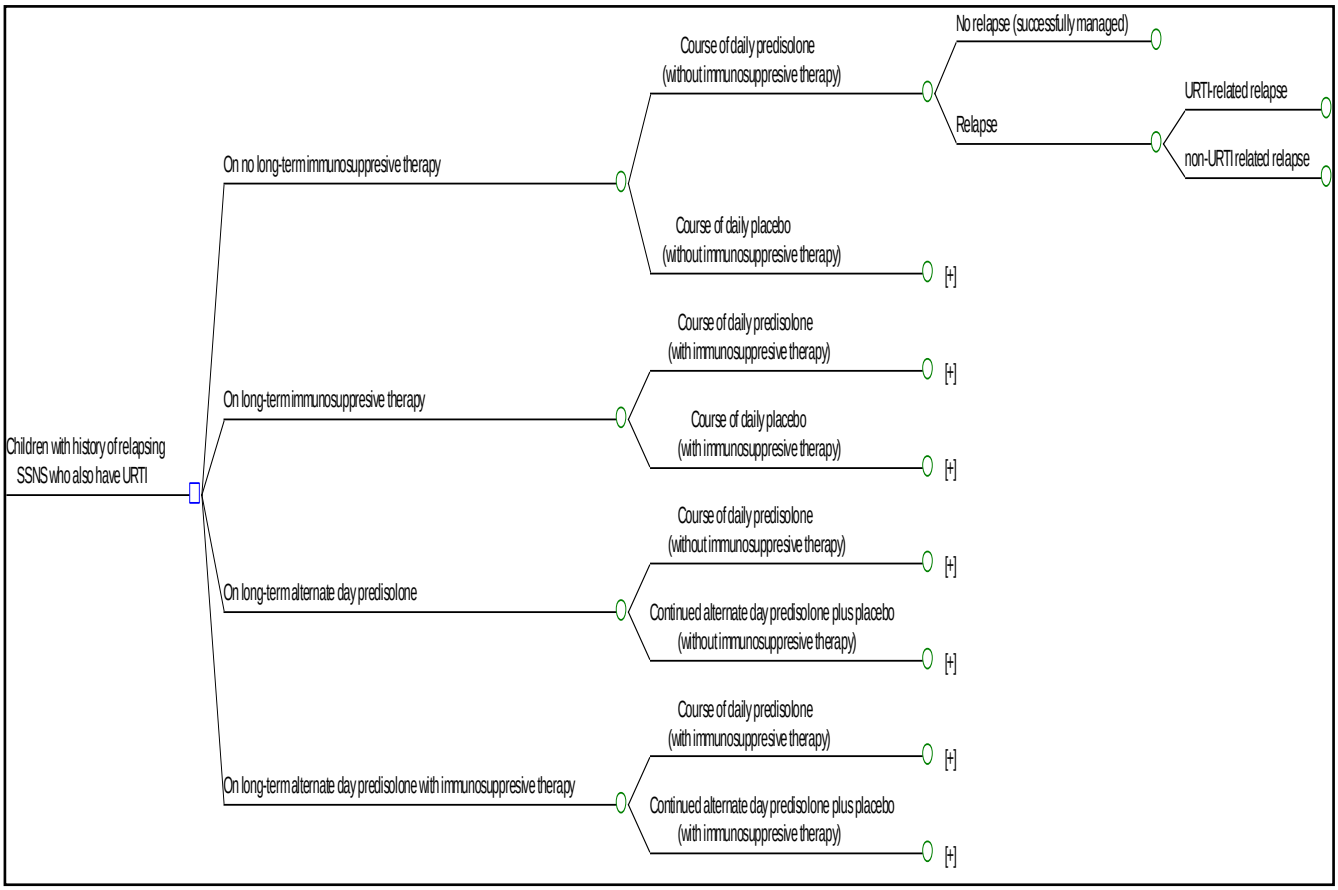
B. Consultation and follow-up costs: routine tests such as blood tests and urinalysis, number of outpatient visits, inpatient visits, and GP visits;

C. Longer term treatment costs (care for long-term adverse effects).

Resource use data such as visits to the subject's GP, hospital (as an outpatient or inpatient) and medicines supplied will be collected using subject-held record books provided for them. This information will be collected at the time of study visits. Due to the economic burden associated with relapse of URTI-related proteinuria that is placed on patients and their families, we will also conduct an economic evaluation that includes private costs such as over the counter medicines and parents' time off work. Resource use data related to these costs will also be collected using patient-held record books. Unit cost data for both NHS and private costs will be derived from nationally representative sources such as the British National Formulary (BNF), the National Schedule for Reference Costs and the Unit Costs of Health and Social Care (PSSRU).

To test the robustness of the conclusions to assumptions made in the modelling, and to sampling variation in the data used in the construction of the model, full deterministic and probabilistic sensitivity analysis will be carried out and results will be reported in terms of incremental cost effectiveness ratios and cost effectiveness acceptability curves. Costs and benefits will be discounted at the standard rate (3.5%).

Figure 1: Indicative decision analytical model



[+] means 'same structure but with appropriate changes in probabilities'.

Figure 1 is a hypothetical illustration of the anticipated modelling approach. The decision tree presents the outcomes that are anticipated to follow either of the two treatment arms (course of daily prednisolone vs. use of placebo tablets such that there is no change to therapy). With each treatment pathway, detailed events will be modelled such as rate of relapse, adverse-effect profile and corresponding cost and quality of life effects. The detailed layout of each treatment pathway will therefore be mapped out once the trial data is collected. At the end of each treatment pathway, cost and quality of life effects will be calculated so that overall cost-effectiveness ratios for the full model can be presented.

The decision analysis model will be constructed using TreeAge Pro software. This is a widely-used and highly user-friendly package ideally suited to the construction and analysis of decision trees and other models.

5.SAFETY ASSESSMENT AND REPORTING

Pharmacovigilance reporting will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006. Annual Development Safety Update Reports (DSURs) will be submitted to the main Research Ethics Committee (REC) and Medicines and Healthcare products Regulatory Agency (MHRA).

The Investigator will assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the Prednisolone Tablet (Wockhardt UK Ltd) Summary of Product Characteristics (SmPC), dated 31/03/2008, section 4.8. This is the Reference Safety Information (RSI) for the study.

Within the PREDNOS 2 trial the steroid prednisolone and the matching placebo are both defined as Investigational Medicinal Products (IMPs).

5.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a (investigational) medicinal product, whether or not related to the medicinal product.

Expected AEs are those listed in the RSI. Information on the current expected events is also given in Appendix 2.

The following are not AEs for the purposes of this trial:

- A pre-existing condition (unless it worsens significantly during treatment)
- Diagnostic and therapeutic procedures, such as surgery (although the medical condition for which the procedure was performed must be reported if new).

The causality and severity of all AEs should be recorded in the medical notes. Only AEs requested on the CRFs should be routinely reported to the PREDNOS 2 Trial Office.

5.2 Assessing Severity and Causality of AEs and SAEs

All AEs and SAEs should be evaluated by a doctor to determine severity and causality between the IMP and/or concomitant therapy and the AE.

The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

An AR is an AE judged by the reporting investigator as having a reasonable causal relationship to a medicinal product. The expression “reasonable causal relationship” means in general that there is evidence or argument to suggest a causal relationship.

5.3 Serious Adverse Events (SAEs)

All events that meet the definition of being Serious Adverse Events (see below) will be reported for the duration of the 12 month study and for 3 months following completion of study drug.

An SAE is any AE that:

- Results in death
- Is life threatening*
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or a birth defect

- Or is otherwise considered medically significant by the Investigator***

*Life-threatening in this context refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more serious.

** Admissions that result in an overnight stay in hospital must be reported. Day admissions do not need to be reported as an SAE.*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Investigators will report all AEs that meet the definition of being serious immediately and within 24 hours of being made aware of the event other than the following events:

Hospitalisations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and has not worsened.

These are expected events and do not require expedited reporting. These events must be reported on the study specific SAE form and sent to the Study Office at the BCTU within one week of the site being made aware the date of hospitalisation.

5.4 Reporting procedure at site

All Serious Adverse Events (SAE) that require expedited reporting should be reported to the Study Office at the BCTU. A trial-specific SAE form should be faxed to the BCTU immediately and within 24 hours of the research staff becoming aware of the event. The Principal Investigator or medically qualified delegate must assess the causality and severity of the event.

The assessment of causality will have 5 categories (unrelated, unlikely to be related, possibly related, probably related and definitely related) within the SAE form for the study. These will map to the binary outcome categorisation of ‘related’ or ‘unrelated’; Unrelated and unlikely to be related will be categorised as “unrelated”, whilst possibly, probably and definitely related will be categorised as related.

To report an SAE to the BCTU office, the Investigator or their delegate(s) must complete, date and sign the study specific BCTU SAE form. The completed form should be faxed or emailed to the BCTU trials team using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form to:

0121 415 9135 and 0121 415 9136 or prednos2@trials.bham.ac.uk

On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number and return this via fax or email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number, the site should contact the BCTU trials team within 1 working day. The site and the BCTU trials team should ensure that the SAE

reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

Where an SAE Form has been completed by someone other than the Investigator, the original SAE form will be required to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

5.4.1 Provision of follow-up information

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a new SAE Form using the SAE reference number provided by the BCTU trials team. Once the SAE has been resolved, all follow-up information has been received and the paperwork is complete, the SAE form that was completed at site must be returned to the BCTU trials office and a copy kept in the Site File.

5.4.2 Reporting procedure at BCTU

On receipt of a faxed SAE form from the site, the BCTU trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. The SAE form (containing the completed unique reference number) will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the TMF.

On receipt of an SAE Form the CI or delegate will independently determine the seriousness and causality of the SAE. An SAE judged by the CI or delegate to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

The CI or delegate will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the approved version of the RSI it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

5.5 Reporting to the Competent Authority and main Research Ethics Committee

5.5.1 Suspected Unexpected Serious Adverse Reactions (SUSARs)

BCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA), main REC and Co-Sponsors within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as non-life threatening SUSARs will be reported within 15 days.

5.6 Reporting all Types of Adverse Events

5.6.1 Reporting Adverse Events/Reactions

Adverse events relating to the patients underlying disease and its treatment will be assessed at each study visit, and recorded on the follow-up CRFs. The BCTU will provide details of all adverse events to the Data Monitoring and Ethics Committee (DMEC) for their review on an annual basis.

5.6.2 Reporting Serious Adverse Events/Reactions

All SAEs (other than those listed in Section 5.3) must be recorded on the SAE form and faxed to the BCTU on 0121 415 9135/6 within 24 hours of the research staff becoming aware of the event. Assessment of causality **must be made by a doctor**. If a doctor is unavailable, initial reports without the causality assessment should be submitted to the BCTU by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter

For each SAE, the following information will be collected:

- Full details in medical terms with a diagnosis, if possible. (Information on the current expected events is given in Appendix 2.)
- Action taken
- Outcome
- Causality, in the opinion of the investigator*

*Assessment of causality **must be made by a doctor**.

SAEs should be reported for the duration of the 12 month study and for 3 months following completion of study drug.

Any SAEs ongoing or still present at the end of the study must be followed up at least until the final outcome is determined, even if this means that follow-up for that patient continues after the study has ended.

5.7 Pharmacovigilance Responsibilities

Local Investigator:

- Medical judgement in assigning seriousness and causality to AEs.
- To fax SAE form to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.
- To sign an Investigator's Agreement accepting these responsibilities.

Chief Investigator (or nominated individual in their absence):

- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment.
- To assess expectedness of SAEs.
- In the event of disagreement between local assessment and Chief Investigator review with regards to SUSAR status, local assessment will not be overruled, but the Chief Investigator may add comments and can upgrade if deemed appropriate prior to reporting to MHRA.

Birmingham Clinical Trials Unit:

- To report SUSARs to MHRA and REC within the required timelines.
- To notify Investigators of all SUSARs.
- To prepare annual safety reports to MHRA, REC, Trial Steering Committee (TSC), and Trial Sponsor.
- To prepare SAE reports for the DMEC at intervals to be decided by the DMEC.

Trial Steering Committee:

- To liaise with the DMEC regarding safety issues.
- The TSC may close the trial on the recommendation of the independent DMEC in the event of clear evidence of harm or benefit for one treatment regimen.

Data Monitoring and Ethics Committee:

- To review the un-blinded overall safety data to identify safety issues which may not be apparent on an individual case basis.
- To review interim analyses.
- To advise the TSC of the safety of the trial.

5.8 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the MHRA in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial.

Sites are therefore requested to notify the Trials Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

6.DIRECT ACCESS TO SOURCE DATA/DOCUMENTS: AUDITING, MONITORING AND INSPECTION

PREDNOS 2 will employ central monitoring of data. This monitoring process will be applied by the BCTU. Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check

incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent data clarification requests for inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group and Trial Steering Committee and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main REC and the (MHRA.

Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. The investigators are required to permit trial-related monitoring, audits, REC review and regulatory inspection(s) providing direct access to source data/documents. Sites are also requested to notify the Trials Office of any MHRA inspections.

7.QUALITY CONTROL AND QUALITY ASSURANCE

7.1 Risk Assessment

A risk assessment will be documented by BCTU. The trial is considered to be Type A = No higher than the risk of standard medical care. All investigators and staff will follow GCP guidelines. This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and all applicable regulatory requirements.

Participants will be aged over 1 year and less than 19 years. Children are considered vulnerable trial subjects, however a trial involving children with relapsing SSNS is ethically justified as the condition is specific to children and the evidence base for treatment used in clinical practice is inadequate. The treatment being used in this trial is used in current clinical practice by some centres and children participating in the trial will face little excess clinical risk, beyond that which the patients would experience in treatment outside of a trial. Prednisolone has been in use for many decades for a wide variety of indications and is standard therapy for the treatment of SSNS. The aim of this study is to try and prevent the development of URTI related relapse, necessitating the commencement of high dose daily prednisolone therapy. There is the risk that this course of action will increase overall steroid exposure without reducing relapse rate. We will be monitoring patients every three months and will carefully document steroid related adverse events, including impact on behaviour. Those children who experience steroid toxicity during the course of the study will have their background immunosuppressive therapy enhanced in an attempt to reduce relapse frequency. There will be no additional study visits for the purposes of the study alone. The three monthly visits are in keeping with routine care in children with relapsing nephrotic syndrome.

Patients aged 16-18 years will be provided with an information sheet and consent form. For children aged under 16, there will be three different information sheets available: one for parents, one for older children and one for younger children. The clinical team will make a decision about which information sheet to use based on their assessment of the

maturity of child and guidance from the parent. The parent's (and patient's if aged 16-18 years) written informed consent to participate in the trial and the child's assent (if under 16 years) as appropriate given the child's competence must be obtained before randomisation and after a full explanation has been given of the treatment options and the manner of treatment allocation.

Participating sites will be provided with guidelines detailing how to conduct the trial and the co-ordinating centre will check that the PI and all staff listed on the delegation log understand these at the Site Initiation prior to commencement of recruitment at the site. Only staff with suitable training and experience (as demonstrated by their current GCP certificate and signed CV) will be listed on the delegation log. Data will be monitored centrally by the trial co-ordination centre.

7.2 Data and Safety Monitoring Plan

An independent DMEC is in place for this trial (see section 2.11). The DMEC will meet annually to review all collected data and may meet more frequently if required after analysis of the available data. The DMEC will advise the Trial Management Committee and the independent TSC on the safety of continuing this clinical trial.

All SUSARs will be reported to the Trial Management Committee and the trial Co-Sponsors (University of Birmingham and Central Manchester University Hospitals NHS Foundation Trust) by facsimile urgently. All data regarding reported adverse events will be made available to the DMEC for review.

8.ETHICAL CONSIDERATIONS

Children are considered vulnerable trial subjects, however a trial involving children with nephrotic syndrome is ethically justified as the condition is specific to children and the evidence base for treatment used in clinical practice is inadequate. It is not possible to perform the study in adult subjects and extrapolate the results to children. The active treatment arm will receive a six day course of daily prednisolone at the time of each URTI which they develop over the 12 month study period. Our hypothesis is that this will reduce the risk of subsequent relapse and reduce the total amount of prednisolone that these subjects are exposed to. There is risk that the hypothesis is incorrect and that these subjects will therefore receive unnecessary additional prednisolone treatment with its attendant adverse effects. The subjects participating in the study will already be receiving significant annual total doses of prednisolone as a result of their relapsing disease and the additional prednisolone administered through their participation in PREDNOS 2 will represent only a relatively small increase in total annual dose. We will carefully monitor adverse effects of prednisolone in this study, including the effect on child behaviour.

Informed consent will be sought from parents and subjects aged 16-18 years. Children of an appropriate age and level of education will be asked to provide signed assent. Information sheets will be provided for parents, subjects aged 16-18 years, older child subjects and younger child subjects.

8.1 Trial Conduct

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical

Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998 and Human Tissue Act 2008 and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol has been submitted to and approved by the main Research Ethics Committee (REC).

Before any patients are enrolled into the trial, local capability and capacity must be confirmed and a clinical trial site agreement between the sponsor and the site must be in place. Sites will not be permitted to enrol patients until written confirmation is received from the Trials Office.

It is the responsibility of the Principal Investigator to confirm that they have read and understood all subsequent amendments, by signing the signature page at the start of each relevant protocol . This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

9.DATA HANDLING AND RECORD KEEPING

9.1 Trial Coordination and Data Management Centre:

Birmingham Clinical Trials Unit, College of Medical & Dental Sciences, Public Health Building, University of Birmingham, Edgbaston, Birmingham B15 2TT
Telephone 0121 415 9132
Fax 0121 415 9135
Email: prednos2@trials.bham.ac.uk

The named clinicians at the participating sites will enter data onto the CRFs. Where this duty is delegated to other staff, this will be recorded in a delegation log.

Data from this trial will be handled by the BCTU, a full-time research facility dedicated to, and with substantial experience in, the design and conduct of randomised clinical trials. The BCTU recognises the responsibilities of a data management centre with respect to the ethical practice of research and the adequate protection of human subjects.

9.2 Confidentiality of Personal Data

The trial will collect personal data about participants, and medical records will be reviewed for all patients and routine physical examinations will be performed.

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. With the parent/patient's consent, their date of birth will be collected at trial entry to assist with long-term follow-up. Patients will be identified using only their unique trial number and date of

birth in mmm/yyyy format on the CRF and correspondence between the Trials Office and the participating site. Patient name, address, postcode, date of birth and parent's telephone numbers will be collected after randomisation on a Clinical Trial Prescription form and faxed, together with the Parent Consent Form, to Birmingham Children's Hospital Pharmacy Department to allow the pharmacy to dispense the study drug and send this directly to the parent's home address. Parents are asked to give permission for the Birmingham Children's Hospital Pharmacy Department to be sent a copy of their signed Informed Consent Form which will not be anonymised. These identifiable personal data will be stored separately from the study record.

Study drug will not be dispensed unless the Birmingham Children's Hospital have received a copy of the consent form and all of the relevant contact details to ensure that study drug is appropriately dispensed and sent to the correct address.

Investigators will keep their own study file logs which link patients with anonymised CRFs. The Investigator must maintain documents not for submission to the Trials Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Trials Office will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer (e.g. Birmingham Children's Hospital Pharmacy Department). Representatives of the PREDNOS 2 trial team may be required to have access to patient's notes for quality assurance purposes, but patients should be reassured that their confidentiality will be respected at all times.

The Study Drug Prescription and Parent Consent Form, which will be sent to the Birmingham Children's Hospital will, out of necessity, contain identifiable personal data. These will be stored separately from the study record. Investigators will keep their own study file logs which link patients with anonymised CRFs

Participants will be informed that their trial data and information will be securely stored at the trial office at the BCTU, and will be asked to consent to this. The data will be stored on a secure computer database, and all personal information obtained for the study will be held securely and treated as strictly confidential. Any data processed outside of the BCTU will be anonymised.

9.3 Long-Term Storage of Data

In line with the Medicines for Human Use (Clinical Trials) Regulations, once data collection is complete on all participants, all data will be retained until the youngest participant reaches the age of 22 or for 5 years after the end of the trial, whichever is the longer.

Any queries or concerns about the data, conduct or conclusions of the trial can also be resolved in this time. Limited data on the participants and records of any adverse events may be kept for longer if recommended by an independent advisory board.

Trial data will be stored within the BCTU under controlled conditions for at least 3 years after closure. Long-term offsite data archiving facilities will be considered for storage after

this time. The BCTU has standard processes for both hard copy and computer database legacy archiving.

10. RESEARCH INDEMNITY

PREDNOS 2 was developed by members of the NIHR Medicines for Children Research Network Nephrology Clinical Studies Group in collaboration with the BCTU and is funded by a grant from National Institute for Health Research Health Technology Assessment programme. The Central Manchester University Hospitals NHS Foundation Trust and the University of Birmingham are the trial co-sponsors. As it is not an industry-sponsored trial, ABPI guidelines on indemnity do not apply and there are no special arrangements for compensation for any non-negligent harm suffered by patients as a result of participating in the study. The normal NHS indemnity liability arrangements for clinician initiated research will, therefore, operate – see NHS Executive Health Service Guidelines HSG (96) 48, 8th November 1996. It should be noted, however, that negligent liability remains the responsibility of the hospital, whether or not a patient is part of a clinical trial, because of the duty of care that the hospital has for their patients.

11. RESEARCH GOVERNANCE

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework for Health and Social Care and the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended in 2006 and any subsequent amendments.

The trial protocol and related documents have been submitted for Research Ethics Committee (REC) approval and Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Agency (MHRA). Any subsequent protocol amendments will also be submitted to the REC and MHRA for approval, as appropriate. Children are considered vulnerable trial subjects, however a trial involving children with nephrotic syndrome is ethically justified as the condition is specific to children and the evidence base for treatment used in clinical practice is inadequate.

11.1 Quality Assurance

Monitoring of this trial will be to ensure compliance with GCP. A risk proportionate approach to the initiation, management and monitoring of the trial will be adopted (as per the MRC/DH/MHRA Joint Project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products) and outlined in the trial-specific risk assessment.

11.2 Sponsor

The Central Manchester University Hospitals NHS Foundation Trust and the University of Birmingham will share responsibilities for co-sponsorship of the trial. The trial is being coordinated by the BCTU at the University of Birmingham. All sites will be required to sign a Clinical Study Site Agreement and Investigator's Agreement, outlining their commitment to accrual, compliance, GCP, confidentiality and publication.

11.3 Trial Organisation

Chief Investigator

Prof Nicholas Webb, Royal Manchester Children's Hospital, Manchester

Co-Investigators

Co-Investigators - Ms Natalie Ives, Dr Emma Frew, Mrs Elizabeth Brettell

University of Birmingham

Dr David Milford, Dr Detlef Bockenhauer, Prof Moin Saleem, Dr Martin Christian, Dr Angela Hall, Dr Ania Koziell, Dr Heather Maxwell, Dr Shivram Hegde, Dr Eric Finlay, Dr Rodney Gilbert, Ms Jenny Booth, Dr Caroline Jones, Dr Karl McKeever, Mrs Wendy Cook

NIHR Medicines for Children Research Network Nephrology Clinical Studies Group

Principal Investigator

Each centre should nominate one person to act as the Local Principal Investigator, who will be responsible for ensuring that all approvals are obtained for their centre and that the clinical trial site agreement is signed and in place. The responsibilities of the local Principal Investigator will be to ensure that all staff who will be involved in the trial are well informed about the trial and trained in trial procedures.

12. FINANCE

PREDNOS 2 is funded by a grant from National Institute for Health Research Health Technology Assessment programme and organised by the Department of Health funded University of Birmingham Clinical Trials Unit.

No individual per patient payment will be made to NHS Trusts, Investigators or patients.

13. COST IMPLICATIONS

PREDNOS 2 has been adopted by the Clinical Research Network (CRN) for Children. This will assist with study site and PI identification and local study set up (Trust R+D approval etc.).

Study drug will be provided free of charge and sent by Royal Mail Special Delivery to the patient's home from the Birmingham Children's Hospital Clinical Trials Pharmacy.

14. TRIAL COMMUNICATIONS

Trial investigators will be informed of trial progress in the form of twice yearly electronic newsletters, annual investigators' meetings and electronic mail (emerging issues).

15. CLINICAL QUERIES

During office hours, the clinical coordinators (see inside front cover for contact details) provide an on-call service for any clinical queries about the trial.

16. PUBLICATION

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of PREDNOS 2 depends on the collaboration of a large number of staff including nephrologists and nurses. For this reason, one individual from each centre which has collaborated in the study will be listed as a contributing author. The Writing Committee will approve all publications using PREDNOS 2 data and the authorship. The Writing Committee will be composed of the Chief Investigator, Co-applicants, BCTU statistical and data analysis staff, and investigators with expertise in clinical and basic science related to childhood nephrotic syndrome.

17. REFERENCES

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MacDonald N, Wolfish N, Maclaine P, et al. Role of respiratory viruses in exacerbations of primary nephrotic syndrome. J Paediatr 1986;108:378-82.

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Medical Research Council. MRC Guidelines for Good Clinical Practice in Clinical Trials. London: MRC; 1998.

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Trompeter RS, Lloyd BW, Hicks J, et al. Long-term outcome for children with minimal change nephrotic syndrome. Lancet 1985;1:368-70.

Webb NJA. Epidemiology and general management of childhood idiopathic nephrotic syndrome. In Evidence-based Nephrology Ed Molony D and Craig J. Blackwell 2008.

18. APPENDIX 1: PREDNOS 2 TRIAL SCHEMA

Identification	Subject identified as attending out-patient appointments at regional paediatric nephrology centre or district general hospital with a diagnosis of steroid sensitive nephrotic syndrome (SSNS)

	"Does the subject have relapsing SSNS, with ≥2 relapses in the preceding 12 months?"	
	↓	
	If yes, "Does the subject meet the inclusion/exclusion criteria?"	If no they are not eligible for the trial
	↓	
	If yes, clinician sends parent and (where age appropriate) subject trial **Parent/Subject Information Leaflets** one to two weeks before next clinic assessment due	
	↓	
Information provision	Parent/subject consider information and have time to discuss trial with family and friends. A contact number will be provided to be used if the parent/subject wants to further discuss the trial prior to their next clinic appointment. Parent/subject considers entering the trial.	Parent/subject is not willing to enter the trial
	↓	
	At next out-patient appointment the trial information is discussed in further detail and the parent/subject have the opportunity to ask any questions they may have about the trial.	Parent/subject is not willing to enter the trial
	↓	
Consent	If parent/subject are willing to enter the trial arrangements made for **Informed Consent/Assent** to be obtained and for baseline assessments **(Baseline Form, CHU-9D, PedsQL, Achenbach and EQ-5D)** to be performed at that same appointment.	
	↓	
Randomisation	Principal Investigator or nominated deputy randomises subject using the **Randomisation Notepad**. Family provided with URTI diagnosis checklist and information on precise study drug dosing regimen by PI using the **Advice to Parents and Participants** sheet. Order supply of study drug using **Prescription Form** from Birmingham Children's Hospital pharmacy. Prednisolone 5mg tablets or matching placebo will be delivered to parent's nominated address. Family provided with clear instructions (printed with back up version sent electronically, if requested) regarding precise regimen to be administered in the event of URTI developing.	
	↓ ↓	
	Subject randomised to active treatment arm. At onset of each URTI, in the following 12 month period, receives 6 days prednisolone. Continues other background immunosuppressive therapy if receiving this.	Subject randomised to control arm. At onset of each URTI, in the following 12 month period, receives 6 days of matching placebo. Continues other background immunosuppressive therapy if receiving this
	↓	
Follow-up	3, 6, 9 and 12 month assessment. Use **Follow-up Form and CHU-9D, PedsQL, Achenbach and EQ-5D** questionnaires dependant on the subject's age. Collect blood for DNA and RNA analysis (single episode). Primary end point (incidence of first URTI-related relapse).	

19. APPENDIX 2: PREDNISOLONE EXPECTED ADVERSE EVENTS

From post-marketing experience, the following side-effect incidences are commonly quoted. The occurrence of drug reactions is generally dose dependent.

Adverse reactions are listed according to the following categories:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)

Prednisolone is associated with the following adverse drug reactions:

Cardiac disorders	
Uncommon:	Oedema, hypertension
Respiratory disorders	
Common	Epistaxis miscellaneous: Diaphoresis
Central nervous system disorders	
Very common	Insomnia, nervousness, behavioural change
Common	Dizziness or light-headedness, headache
Uncommon	Hallucinations, seizures
Eye disorders	
Common	Cataracts, glaucoma
Gastrointestinal disorders	
Very common	Increased appetite, indigestion
Musculoskeletal and connective tissue disorders	
Uncommon	Fractures, muscle-wasting, osteoporosis
Endocrine and metabolic disorders	
Common	Diabetes mellitus, glucose intolerance, hyperglycemias, reduced growth velocity, Cushingoid facies
Uncommon	Cushing's syndrome, pituitary-adrenal axis suppression, pancreatitis
Dermatologic conditions	

Common	Hirsutism, hypo pigmentation, striae, acne
Neuromuscular and skeletal	
Common	Arthralgia

Prednisolone is also associated with the following SAEs – predominantly in adult patients:

- Musculoskeletal: insufficiency fractures, avascular osteonecrosis
- Cardiovascular: premature atherosclerosis, myocardial infarction
- Gastrointestinal: ulceration and bleeding
- Central nervous system: psychosis
- Endocrine: hyperosmolar non-ketotic state, Addisonian crisis
- Miscellaneous: Bacterial infections, fungal infections, viral infections, ocular herpes zoster.

20. APPENDIX 3: PREDNOS 2 UNBLINDING OF PATIENTS

PREDNOS 2 Clinical Trial

Code-break/Unblinding of Patients Procedure

Background

In the event of a medical emergency it may be important for the doctor to be aware of which treatment has been used for the patient and it may be necessary for the trial code to be broken and the treatment allocation to be revealed.

When <u>not</u> to unblind:

1. There should be no need for unblinding if the patient is not currently taking a 6 day course of prednisolone following a URTI, as unblinding would be extremely unlikely to influence the choice of treatment for, or prognosis of, any condition in the patient. Hence any request for unblinding during when the patient is not taking a 6 day course of prednisolone following a URTI should be referred to the Chief or Principal Investigators.

When to unblind:

1. When patient is taking study treatment, i.e. when they are taking a 6 day course of prednisolone following a URTI, unblinding should only occur when there is a clinical need to know whether the patient is receiving prednisolone, as this information is required to decide on the patient's treatment.

   e.g. i) the patient develops a condition where oral or i.v. prednisolone therapy is indicated, e.g. severe asthma.

   ii) the patient develops a condition where the prednisolone may need to be changed or is relevant to determining treatment, for example where a severe infection develops.

How to unblind?

1. If the PI or co-investigator decides it is necessary to unblind the patient, please request the unblinding from the Senior Clinical Trials Technician or Lead Pharmacist for Clinical Trials at Birmingham Children's Hospital Pharmacy:
   a. Tel: **0121 333 9308** (during pharmacy opening hours)
   b. Tel: **0121 333 9999** (outside pharmacy opening hours contact the on-call pharmacist through the hospital switchboard)

2. The pharmacist will record the name, post, address and contact number of the person requesting the unblinding. They will also require patient ID, name and the reason for unblinding request.

21. APPENDIX 4: PREDNOS 2 QUESTIONNAIRES TABLE OF COMPLETION BY AGE

PREDNOS 2 Questionnaires Table of Completion by Age

Age of Child (yrs)	Parent Completed Peds QL	Parent Completed Child Health Utility (CHD) 9D	Parent Completed Achenbach Childhood Behaviour Checklist	Parent completed EQ-5D
>1-1.5	No form available	No form available	No form available	No form available
1.5-2	No form available	No form available	Use version 1.5-5 yrs	No form available
2	Use version 2-4yrs	No form available	Use version 1.5-5 yrs	No form available
3	Use version 2-4yrs	No form available	Use version 1.5-5 yrs	No form available
4	Use version 2-4yrs	No form available	Use version 1.5-5 yrs	No form available
5	Use version 5-7yrs	Use CHU-9D	Use version 1.5-5 yrs	No form available
6	Use version 5-7yrs	Use CHU-9D	Use version 6-18 yrs	No form available
7	Use version 5-7yrs	Use CHU-9D	Use version 6-18 yrs	No form available
8	Use version 8-12 yrs	Use CHU-9D	Use version 6-18 yrs	No form available
9	Use version 8-12 yrs	Use CHU-9D	Use version 6-18 yrs	No form available
10	Use version 8-12 yrs	Use CHU-9D	Use version 6-18 yrs	No form available
11	Use version 8-12 yrs	Use CHU-9D	Use version 6-18 yrs	No form available
12	Use version 8-12 yrs	Use CHU-9D	Use version 6-18 yrs	Use EQ-5D
13	Use version 13-18yrs	Use CHU-9D	Use version 6-18 yrs	Use EQ-5D
14	Use version 13-18yrs	Use CHU-9D	Use version 6-18 yrs	Use EQ-5D
15	Use version 13-18yrs	Use CHU-9D	Use version 6-18 yrs	Use EQ-5D
16	Use version 13-18yrs	Use CHU-9D	Use version 6-18 yrs	Use EQ-5D
17	Use version 13-18yrs	Use CHU-9D	Use version 6-18 yrs	Use EQ-5D
18	Use version 13-18yrs	Use CHU-9D	Use version 6-18 yrs	Use EQ-5D