

PROTOCOL

Full Title: Long-term tapering versus standard prednisolone (steroid) therapy for the treatment of the initial episode of childhood nephrotic syndrome: national multicentre randomised double blind trial

Short Title: PREDnisolone in Nephrotic Syndrome: The PREDNOS study

EudraCT number – 2010-022489-29

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Ethical Approval: North West 7 Research Ethics Committee Ref. No. 10/H1008/122

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Trial Co-Sponsors – University of Birmingham and Central Manchester University Hospitals NHS Foundation Trust

Sponsor's Project number – RG_08-015

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Protocol Version 2.2

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Signature page

PREDNOS Trial Protocol Version 2.2, 11th June 2014

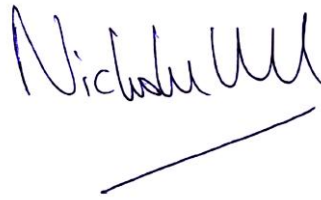
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This protocol has been approved by:

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Trial Role: Chief Investigator

Signature:

A handwritten signature in blue ink, appearing to read 'Nicholas Webb', with a long horizontal line underneath it.

Date:

11th June 2014

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

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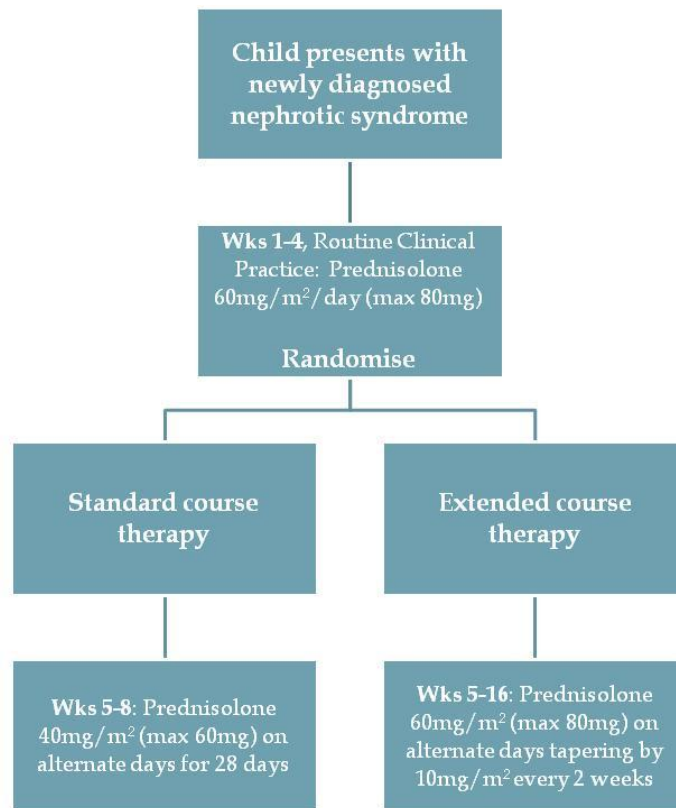
Protocol Synopsis

Title	Long-term tapering versus standard prednisolone (steroid) therapy for the treatment of the initial episode of childhood nephrotic syndrome: national multicentre randomised double blind trial
Short Title	PREDnisolone in NephroTic Syndrome: The PREDNOS study
Clinical Phase	III
Chief Investigator	Prof Nicholas Webb, Royal Manchester Children's Hospital, Manchester
Co-Chief Investigator	Dr Richard Trompeter Great Ormond Street Hospital, London
Trial Co-Sponsors	University of Birmingham and Central Manchester University Hospitals NHS Foundation Trust
Funding	National Institute for Health Research Health Technology Assessment programme
Sample Size	236
Accrual Period	40 months
Follow-up period	All patients will be followed up for at least 24 months and for a variable time period beyond 24 months until the end of the trial
Study Duration	5 years 10 months
End of trial definition	The end of trial will be 6 months after the last data capture. The last data capture will be 2 years following recruitment of the last patient. 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 compare an extended course (sixteen week) tapering prednisolone regimen with the standard eight week regimen as originally proposed by the International Study of Kidney Disease in Children (ISKDC).
Primary Study Objectives	To determine whether an extended course of prednisolone increases the time to first relapse in children presenting with steroid sensitive nephrotic syndrome
Primary Outcome Measures	Time to first relapse. Relapse of proteinuria is defined by Albustix positive proteinuria (+++ or greater) for 3 consecutive days or the presence of generalised oedema plus 3+ proteinuria.
Secondary Study Objectives	To determine whether an extended course of prednisolone

	<p>i] reduces relapse rate</p> <p>ii] reduces the proportion of children who develop frequently relapsing or steroid dependent disease</p> <p>iii] reduces the requirement for second and third line immunosuppressive agents including levamisole, cyclophosphamide, ciclosporin, tacrolimus and mycophenolate mofetil</p> <p>iv] is associated with an increased incidence of steroid-related adverse events including behavioural problems</p> <p>v] is more cost effective than standard course therapy</p>
Secondary Outcome Measures	<p>i] Relapse rate</p> <p>ii] Incidence of frequently relapsing steroid sensitive nephrotic syndrome (defined as 2 relapses or more in the first six months following presentation or 4 relapses within any 12 month period)</p> <p>iii] Incidence of steroid dependent nephrotic syndrome (defined as relapses on or within 14 days of completion of steroid therapy) nephrotic syndrome</p> <p>iv] Incidence of use of second line immunosuppressive agents, including levamisole, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil and rituximab</p> <p>v] Incidence of serious adverse events</p> <p>vi] Incidence of adverse events</p> <p>vii] Incidence of behavioural change (as assessed by the Achenbach child behaviour checklist)</p> <p>viii] Cost per relapse of proteinuria</p> <p>ix] Cost per QALY gained</p>
Inclusion Criteria	<p>Children presenting with the first episode of steroid sensitive NS who meet all of the following criteria:</p> <ul style="list-style-type: none"> • Urine albumin: creatinine ratio > 200mg/mmol or protein: creatinine ratio >200mg/mmol, determined quantitatively on an early morning urine sample • Serum/plasma albumin level < 25g/L • Age over 1 year and less than 15 years at the time of diagnosis • No prior therapy with steroids, immunosuppressive or cytotoxic agents for any form of renal disease (other than the 28 days of prednisolone therapy given initially as routine clinical practice) • No evidence of underlying systemic disorder or exposure to agents known to be associated with newly presenting steroid sensitive nephrotic syndrome • Informed consent
Exclusion Criteria	<ul style="list-style-type: none"> • Children with histological changes other than minimal lesion glomerulonephritis where renal

	<p>biopsy has been undertaken</p> <ul style="list-style-type: none"> • Children with a prior history of poor compliance with medical therapy • Known allergy to prednisolone
Treatment description/arms	<p>Standard course therapy: Weeks 1 - 4, Prednisolone 60mg/m²/day (max 80mg), Weeks 5 - 8: Prednisolone 40mg/m² (max 60mg) on alternate days for 28 days.</p> <p>Extended course therapy: Weeks 1 - 4, Prednisolone 60mg/m²/day (max 80mg), Weeks 5-16: Prednisolone 60mg/m² (max 80mg) on alternate days tapering by 10mg/m² every 2 weeks</p>
Primary Analyses	Time to first relapse of the patients in the extended course prednisolone arm compared with the standard course prednisolone arm
Secondary Analyses	<p>Comparison between extended and standard course arms relating to;</p> <p>i] relapse rate</p> <p>ii] proportion of children who develop frequently relapsing or steroid dependent disease</p> <p>iii] proportion who require treatment with second and third line immunosuppressive agents including levamisole, cyclophosphamide, ciclosporin, tacrolimus and mycophenolate mofetil</p> <p>iv] proportion who develop and severity of steroid-related adverse events including behavioural problems</p> <p>v] Economic evaluation of cost per relapse and cost per QALY gained</p>
Exploratory objectives	<p>A single 10ml sample of blood will be collected for DNA extraction. This will be used to</p> <p>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 Kleita, Great Ormond Street Hospital and Institute of Child Health, University College, London)</p> <p>ii] Perform DNA methylation studies (in collaboration with Dr Rachel Lennon and Professor David Ray, University of Manchester)</p>
Safety Monitoring	<p>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).</p> <p>An independent Data Monitoring Committee (DMC) will review adverse event data annually or more frequently if requested by the DMC.</p>

Study Schema



(Also see Appendix 1: Trial Schema)

Index

1.	SUMMARY	11
1.1	Pilot trial.....	12
2.	GENERAL INFORMATION	12
2.1	Study Co-Sponsors	12
2.2	Ethical approval	13
2.3	EudraCT number	13
2.4	MHRA Clinical Trials Authorisation	13
2.5	UK Medicines for Children Research Network.....	13
2.6	Chief Investigator.....	13
2.7	Co-Chief Investigator.....	13
2.8	Co-Investigators	13
2.9	Name and address of trial co-ordinator and co-ordinating centre	13
2.10	Trial Steering Committee	14
2.11	Trial Management Committee	15
2.12	Data Monitoring Committee	16
2.13	Sponsor’s medical expert for the trial	16
2.14	Protocol and protocol amendments	16
2.15	Services Involved	16
3.	BACKGROUND.....	17
3.1	Study rationale / introduction	17
3.2	Research question.....	17
3.3	Investigational medicinal product.....	18
3.4	Name of supplier	18
3.5	Summary of known and potential risks and benefits.....	18
3.6	Trial conduct.....	18
4.	TRIAL DESIGN.....	18
4.1	Introduction.....	18
4.2	Inclusion criteria.....	20
4.3	Exclusion criteria	20
4.4	Early withdrawal from study.....	20
4.5	The Research Setting.....	21
4.6	Study flow chart	22
4.7	Study visit schedule.....	23
4.8	Recruitment	24
4.9	Patient and carer information leaflet	24
4.10	Informed Consent	24
4.11	Randomisation.....	25
4.12	Trial treatment	26
4.13	Concomitant medications	26
4.14	Follow-up assessments	26

4.15	Study visits	27
4.16	Data Collection	28
4.17	Outcome Measures	29
4.17.1	Primary study endpoint:	29
4.17.2	Secondary endpoints/ outcome measures:	29
4.18	Monitoring of prednisolone related adverse effects	29
4.19	Stopping rules and unblinding	30
4.20	Blood sample collection for DNA isolation and substudies	31
4.20.1	Genome-wide association study of steroid sensitive nephrotic syndrome ..	31
4.20.2	Investigation of DNA methylation	31
4.21	Sample size	32
4.22	Statistical Analysis.....	32
4.23	Health Economic analysis	33
4.24	Vaccination	34
5.	SAFETY ASSESSMENT AND REPORTING	35
5.1	Definitions of Types of Adverse Events	35
5.2	Adverse Events (AEs)	35
5.3	Adverse Reactions (ARs)	36
5.4	Serious Adverse Events (SAEs).....	36
5.5	Serious Adverse Reactions (SARs).....	37
5.6	Suspected Unexpected Serious Adverse Reactions (SUSARs).....	37
5.7	Assessing Severity and Causality of AEs and SAEs	37
5.8	Reporting all Types of Adverse Events.....	37
5.8.1	Reporting Adverse Events/Reactions	37
5.8.2	Reporting Serious Adverse Events/Reactions	37
5.8.3	Reporting SUSARs	38
5.9	Pharmacovigilance Responsibilities	38
5.10	Notification of Serious Breaches.....	39
6.	DIRECT ACCESS TO SOURCE DATA/DOCUMENTS: AUDITING, MONITORING AND INSPECTION	40
7.	QUALITY CONTROL AND QUALITY ASSURANCE.....	40
7.1	Risk Assessment.....	40
7.2	Data and Safety Monitoring Plan	40
8.	ETHICAL CONSIDERATIONS	41
8.1	Trial Conduct	41
9.	DATA HANDLING AND RECORD KEEPING.....	41
9.1	Trial Coordination and Data Management Centre:	41
9.2	Confidentiality of Personal Data	42
9.3	Long-Term Storage of Data.....	42
10.	RESEARCH INDEMNITY	43
11.	RESEARCH GOVERNANCE	43
11.1	Sponsor	43
11.2	Trial Organisation	43

12.	FINANCE.....	44
13.	COST IMPLICATIONS	44
14.	TRIAL COMMUNICATIONS.....	44
15.	CLINICAL QUERIES	44
16.	PUBLICATION.....	44
17.	REFERENCES.....	45

1. SUMMARY

Idiopathic nephrotic syndrome (NS) is the commonest glomerular disorder of childhood with an incidence of 2-4 cases per 100,000 children in the UK. Around 80% of cases are due to minimal change disease (MCD) and the majority will respond to corticosteroid (prednisolone or prednisone) therapy^{1,2}. Nephrotic syndrome is a condition marked by very high levels of protein in the urine; low levels of protein in the blood; swelling, especially around the eyes, feet, and hands; and high blood cholesterol levels. Whilst steroid sensitive NS is considered to be a relatively benign condition in that progression to end stage renal failure is extremely rare and over 80% enter spontaneous long term remission in later childhood, the early disease is characterised by a relapsing course. This places the child at risk of acute complications such as infection, hypovolaemia and thrombosis. In addition, frequent relapses result in the administration of further courses of corticosteroids with their attendant adverse effects or the prescription of more potent immunosuppressive therapies including alkylating agents to control the disease³.

There is emerging evidence from a Cochrane review⁸ that intensification of the initial corticosteroid therapy at disease presentation may reduce the subsequent relapse rate. It is however unclear whether there was a clinically useful reduction in the incidence of steroid dependent disease and the use of second-line immunosuppressive agents. Furthermore, the studies reported somewhat different adverse-effects, making interpretation of the impact of increased duration of steroid therapy on adverse-effect profile difficult. In light of this, there is no national or international consensus regarding what the ideal steroid regimen at disease presentation should be. An appropriately designed and powered trial that will allow a definite statement to be made regarding the ideal course of corticosteroid therapy in British children is therefore required.

A 55 patient pilot study comparing an extended 16 week tapering course of prednisolone with 8 weeks of prednisolone therapy (as originally proposed by the International Study of Kidney Disease in Children (ISKDC)) using a double-blind placebo-controlled methodology has recently been completed. This pilot study has

- Provided “proof of principle” on successful recruitment and collaboration.
- Provided information on recruitment rates.
- Provided further evidence on the incidence of trial outcomes that have been used to inform definitive trial design. These outcomes include: sustained remission at 6 and 12 months; time to relapse; frequently relapsing disease; serious adverse events; need for other immunomodulatory and immunosuppressive medications.

This definitive trial will use identical methodology to the pilot study: we will compare an extended course (16 week) tapering prednisolone regimen with the standard 8 week course as originally proposed by the ISKDC. Close attention will be paid to the development of adverse effects of prednisolone therapy, including cosmetic and behavioural changes.

As a development of the protocol following completion of the pilot trial, this study will also;

- i] collect detailed information on quality of life and health outcomes to allow a comprehensive health economic analysis to be performed

- ii] collect a single blood 10ml sample from study participants for the isolation of DNA.

Using genome wide association study methodology we will search for a potential gene for steroid sensitive nephrotic syndrome and also identify potential candidate genes which might influence response to steroid therapy and the development of adverse effects.

Further studies will investigate DNA methylation mechanisms.

1.1 Pilot trial

The pilot study recruited its first patient in August 2006. A total of 55 patients (33 male) were recruited by June 2008. Trial recruitment was facilitated by the adoption of the study by UK Medicines for Children Research Network (MCRN) in March 2007. A successful collaborative trial network was established, with principal investigators appointed at a total of 37 sites. By study completion, a total of 26 sites were fully set-up and 18 had recruited patients. A further 13 had expressed active interest in participation in the study.

Of the 55 children recruited, the mean age was 5.5 years. Thirty-nine were of White British ethnic origin, 12 South Asian, 2 each of either mixed racial or other racial origin. This reflects the known six-fold increased incidence of the disease in the UK South Asian population.

Two children proved resistant to steroid therapy after informed consent, though prior to starting trial medication. Two experienced difficulties in taking solid tablets and withdrew from the study and one patient changed their area of residence and was lost to follow-up. A full-analysis set of 50 patients was therefore identified.

A decision has been made to not unblind these pilot data, but to add them to the data set collected in the main trial. However, analysis of the pooled data has shown that 36 out of 50 patients had relapsed before 12 months follow-up, a relapse rate of 72% (95% confidence interval 58% to 83%). Relapses were initially treated with prednisolone, though the development of multiple relapses resulted in a total of five children being commenced on alternative immunosuppressive agents including; levamisole (3), cyclophosphamide (1) and methylprednisolone (1).

There were no serious unexpected suspected adverse reactions (SUSARs). Three children experienced serious adverse events (SAEs) (trapped finger requiring stitching in theatre, abdominal pain requiring hospitalization and viral induced wheezing requiring hospitalization).

2. GENERAL INFORMATION

2.1 Study Co-Sponsors

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2.2 Ethical approval

The study has been approved by the North West 7 Research Ethics Committee 10/H1008/122.

2.3 EudraCT number

2010-022489-29

2.4 MHRA Clinical Trials Authorisation

21761/0255/001-0001

2.5 UK Medicines for Children Research Network

The study will be submitted for adoption by the UK Medicines for Children Research Network

2.6 Chief Investigator

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2.8 Co-Investigators

Dr Carole Cummins
Professor Keith Wheatley
Miss Natalie Ives
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2.9 Name and address of trial co-ordinator and co-ordinating centre

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2.14 Protocol and protocol amendments

Any changes will be authorised by the Chief Investigator, Prof Nicholas Webb and approved by the MHRA and NRES.

2.15 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

The ideal initial corticosteroid regimen at presentation of childhood nephrotic syndrome should rapidly induce urinary remission with resolution of oedema. It must be sufficient to prevent frequent relapses necessitating the use of second-line agents, though not so intensive that serious adverse-effects develop. The first standardised corticosteroid treatment regimen was introduced by the ISKDC in the 1960s and consisted of prednisone 60mg/m² (maximum 80mg) given daily for 4 weeks followed by 40mg/m² (maximum 60mg) on 3 consecutive days out of seven for a total of 4 weeks⁴. Many centres made a minor modification whereby 40mg/m² was given on alternate days during the second four-week period, a regimen which is still in widespread use ("standard regimen"). There is emerging evidence that more intensive treatment at disease presentation may reduce the subsequent relapse rate^{5,6}.

A Cochrane review⁷ concludes that intensification of the initial corticosteroid therapy at disease presentation may reduce the subsequent relapse rate. Children who receive 3 months or more steroid therapy at disease presentation appear to have a significantly higher relapse-free rate at 12 months post-presentation than those who receive the standard regimen⁷, but there were concerns over trial quality. It is also unclear whether there was a clinically useful reduction in the incidence of steroid dependent disease and the use of second-line immunosuppressive agents. Furthermore, the studies reported somewhat different adverse-effects, making interpretation of the impact of increased duration of steroid therapy on adverse-effect profile difficult. In light of this, there is no national or international consensus regarding what the ideal steroid regimen at disease presentation should be.

Although six trials compared a standard regimen with three months or longer duration of treatment, there were concerns over the methodological quality of several trials and the trials were not blinded. The Cochrane authors commented that further high quality RCTs are necessary and this trial has been discussed with them. The optimal total dose and duration of therapy that is most beneficial in terms of maintaining long-term remission with the lowest incidence of adverse-effects is still undetermined. The previously performed studies consist of small number of patients and none have systematically and objectively looked at the wide range of steroid-induced adverse events. Therefore, there is little national or international consensus regarding the best way to treat children with nephrotic syndrome at disease presentation.

An appropriately designed and powered trial that will allow a definite statement to be made regarding the ideal course of corticosteroid therapy in British children is required. A pilot study comparing the standard eight week regimen with a 16 week tapering prednisolone regimen has recently been completed. As outlined above, this pilot study proved successful and we are now in a position to move forward to this definitive trial.

3.2 Research question

This study will compare an extended course (sixteen week) tapering prednisolone regimen with the standard eight week regimen as originally proposed by the International Study of Kidney Disease in Children (ISKDC). The purpose of the study is to determine whether this extended course of prednisolone increases time to first relapse in children presenting with steroid sensitive nephrotic syndrome and whether this is associated with an increased incidence of prednisolone-related adverse events.

3.3 Investigational medicinal product

Prednisolone is a licensed corticosteroid immunosuppressant. Patients will receive standard prednisolone supplied by their treating hospital, in accordance with routine clinical practice, for the first four weeks. For the remaining twelve weeks, patients recruited into the study will receive 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.

3.5 Summary of known and potential risks and benefits

Please always use the most recent updated SmPC. Up-to-date SmPCs of licensed products are available at <http://emc.medicines.org.uk/>. Please see Appendix 2 for Prednisolone Expected Adverse Events.

IMPs will only be used for trial patients.

3.6 Trial conduct

This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

4. TRIAL DESIGN

4.1 Introduction

Design: Double blind randomised controlled trial (RCT)

Population to be studied: Children with steroid sensitive nephrotic syndrome

Current therapy: Current **standard course therapy** is prednisolone 60mg/m²/day (maximum 80mg) for four weeks followed by 40mg/m² (maximum 60mg) on alternate days for a further four weeks (Table 1).

Alternative therapy: The proposed alternative **extended course therapy** also commences with prednisolone 60mg/m²/day (maximum 80mg) for four weeks, but the prednisolone is reduced more gradually over a further twelve weeks (Table 1).

At disease presentation, all children will be treated in accordance with existing national protocols with prednisolone 60mg/m² (maximum 80mg) daily in an open label manner to ascertain whether they are steroid sensitive and as such eligible for recruitment into the study. We will ask all centres recruiting patients into the study to attempt to standardise the prednisolone preparation which they use in all newly presenting children to ensure uniformity during this initial four week period. We will recommend that non-enteric coated prednisolone tablets should be used, these being crushed for smaller children and others that are unable to swallow tablets whole. Tablet crushers will be provided by the coordinating centre to study sites so that these can be used where necessary. Whilst the use of soluble and enteric-coated prednisolone should be discouraged during initial four week open label treatment, children so treated are still eligible for recruitment into the study.

Recruitment and randomisation will occur during this initial four week period, whilst children are receiving prednisolone 60mg/m² (maximum 80mg) daily in accordance with routine clinical practice. This allows adequate time for the principal investigator to discuss the study with the child and their family and to obtain fully informed consent, at the same time ensuring that the patient has become, or is likely to become, corticosteroid sensitive as defined by the resolution of proteinuria on routine dipstick analysis (zero or trace proteinuria for three consecutive days), and as such, eligible for recruitment. It is anticipated that the majority of recruitment will occur during week three of open label routine clinical treatment; at this point the majority of children with steroid sensitive nephrotic syndrome will have responded to prednisolone and therefore be eligible. Randomisation will not therefore be performed until the 4th week of open label routine clinical treatment, leaving this as close as possible to the point at which randomised treatments commence (following completion of four weeks of routine clinical treatment), but still allowing sufficient time for the study drug to be delivered to the family home in time for commencement at the beginning of week 5 of treatment.

The randomised study drug regimen will commence at the beginning of week 5 of treatment (day 29). The study is double blinded through the use of prednisolone 5mg and matching placebo tablets and children in both treatment arms will receive the same number of tablets at any time-point in the study. No 1mg, 25mg or 50mg prednisolone tablets will be used in the study. For children unable to swallow tablets whole the prednisolone and placebo tablets can be crushed using a tablet crusher which will be supplied by the prescriber during the open-label routine clinical treatment. The entire study drug regimen (week 5 to 16) will be dispensed within monitored dose packs containing either active drug or active drug and placebo tablets according to the regimen to which the patient is randomised. These will be sent directly to the patient's home or an alternative address agreed with the patient's legal representative from the Birmingham Children's Hospital Trials Pharmacy using the Royal Mail Special Delivery Service. All doses will be given as a single morning dose with breakfast.

Table 1: Standard and extended course therapy

Time (weeks)	Standard course therapy Prednisolone dose	Extended course therapy Prednisolone dose
	OPEN LABEL ROUTINE CLINICAL TREATMENT	OPEN LABEL ROUTINE CLINICAL TREATMENT
0-4	60mg/m ² /day (max 80mg)	60mg/m ² /day (max 80mg)
	RANDOMISED PHASE	RANDOMISED PHASE
5-6	40mg/m ² (+ placebo*) on alternate days	60mg/m ² on alternate days
7-8	40mg/m ² (+ placebo*) on alternate days	50mg/m ² on alternate days
9-10	Placebo on alternate days	40mg/m ² on alternate days
11-12	Placebo on alternate days	30mg/m ² on alternate days
13-14	Placebo on alternate days	20mg/m ² on alternate days
15-16	Placebo on alternate days	10mg/m ² on alternate days

*Placebo is added here to maintain the double blind so that there is no difference in the number of tablets taken between the standard and long-term tapering regimens.

Monitored dose packs will be made up with the entire daily dose contained within the compartment (prednisolone alone, prednisolone plus placebo or placebo alone, depending upon time post diagnosis)

Every patient participating in the study will be issued with a standard pack containing

- i. Patient diary in which the results of the morning urinalysis, treatment administration and any consultations with healthcare professionals (GP, nurse, hospital A+E department etc) and details of medicines prescribed or purchased over the counter are to be recorded
- ii. Bottle of urinalysis sticks (Albustix, Bayer Diagnostics).

This pack will be sent to the family by the Birmingham Children's Hospital Pharmacy following enrolment into the study. Trial medication labelling will comply with the applicable regulatory requirements and Clinical trial specific labels will be attached to all treatment packs prior to dispensing. Drug accountability will be according to local policy at the Birmingham Children's Hospital Pharmacy.

4.2 Inclusion criteria

- Children presenting with the first episode of steroid sensitive NS who meet all of the following criteria:
- Urine albumin: creatinine ratio > 200mg/mmol or protein: creatinine ratio >200mg/mmol, determined quantitatively on an early morning urine sample.
- Serum/plasma albumin level < 25g/L
- Age over 1 year and less than 15 years at the time of diagnosis (children of 15 years and above have been excluded because of the reduced likelihood of their nephrotic syndrome being steroid sensitive and the increased likelihood of 'adult' causes of nephrotic syndrome).
- No prior therapy with steroids, immunosuppressive or cytotoxic agents for any form of renal disease (other than the 28 days of prednisolone therapy given initially as routine clinical practice)
- No evidence of underlying systemic disorder or exposure to agents known to be associated with newly presenting steroid sensitive nephrotic syndrome
- Informed consent

4.3 Exclusion criteria

- Children with histological changes other than minimal lesion glomerulonephritis where renal biopsy has been undertaken
- Children with a prior history of poor compliance with medical therapy.
- Known allergy to prednisolone

4.4 Early withdrawal from study

Children who are found to be resistant to steroid therapy (no clinical response after 28 days of daily prednisolone at 60mg/m²/day) following recruitment and randomisation will be withdrawn from the study. It is anticipated that the large majority of children will have shown a response to prednisolone therapy (defined as three consecutive days of zero or

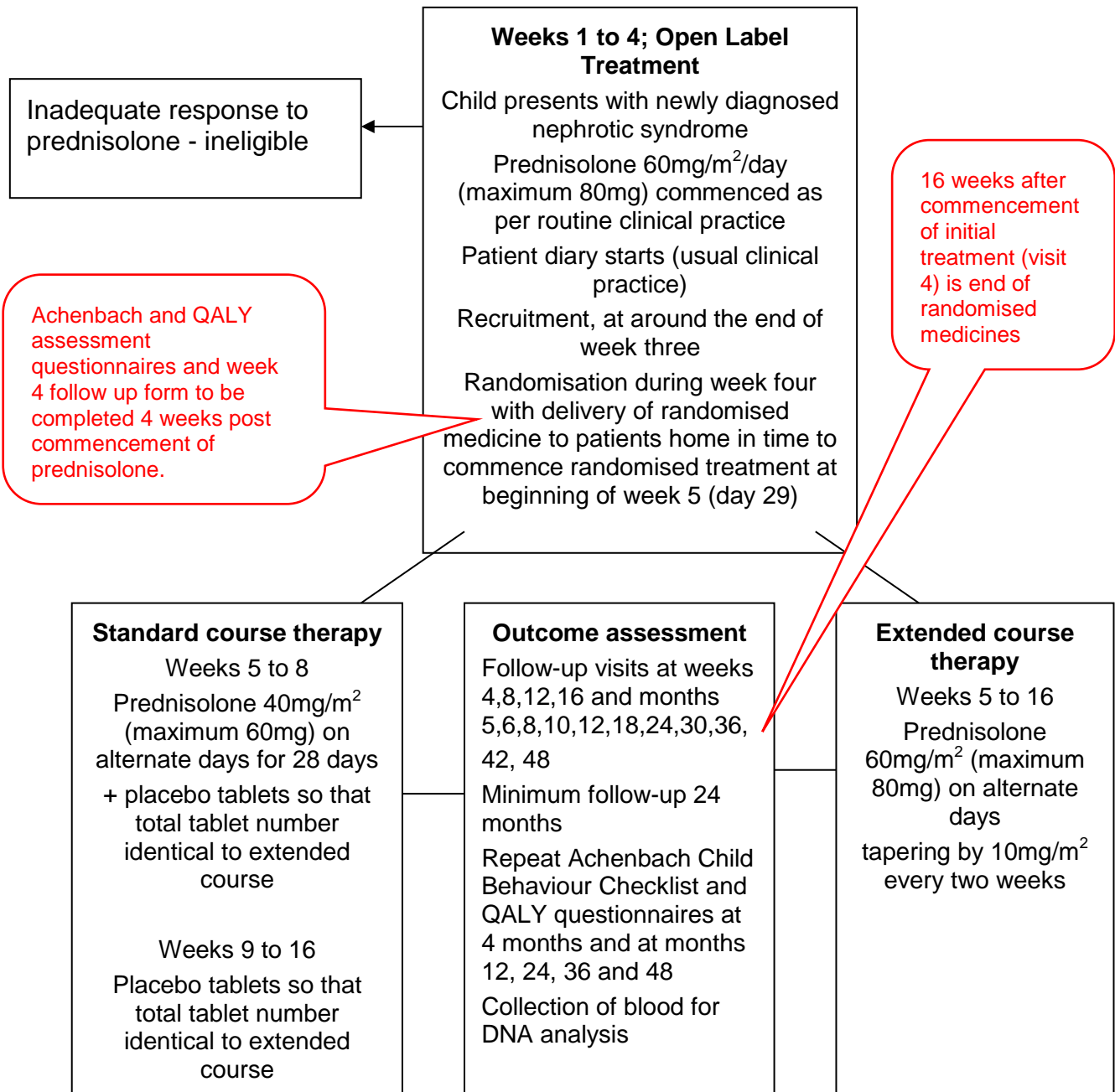
trace proteinuria on urine dipstick analysis) by the time of their recruitment into the study. There may, however, be a small number of children recruited at around day 21 prior to the establishment of steroid responsiveness; where these children have undergone randomisation but remain steroid unresponsive by day 28 then the child will be withdrawn from the study. This will be notified to the trial office and discussed with the Chief Investigator

4.5 The Research Setting

Patients will be recruited, randomised and followed-up in district general hospitals and tertiary paediatric nephrology units. There may be a number of different arrangements made for recruitment and follow up. Generally the same consultant or his/her nominated deputy will recruit and follow up the patient, but a number of referral and shared care arrangements are acceptable. Some tertiary nephrology units do not generally see first episode patients unless the clinical course is atypical or complicated, but a small number of district centres may request that recruitment and follow-up take place in the regional paediatric nephrology centre. Some paediatricians at local hospitals may refer to tertiary centres, but share follow-up. Some paediatric nephrologists may recruit patients at peripheral clinics at district general hospitals and in this case the local paediatrician will often share follow up of the patient.

The study has been endorsed by the British Association for Paediatric Nephrology and paediatric nephrologists in the tertiary centres will act in an advisory role and will provide advice for centres within their own region: We aim to involve all regions of the UK. The pilot study was adopted by the UK Medicines for Children Research Network (MCRN) and this full study will also be submitted for adoption. There is ongoing expansion of the MCRN local research networks to provide support for those centres that were previously not included and it is anticipated that the large majority of centres will now receive MCRN support. Where such arrangements are not in place, the support of the CLRN will be sought and further support provided by study coordinating centre in Birmingham.

4.6 Study flow chart
Figure 1



4.7 Study visit schedule

Table 2

Visit	Randomisation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Weeks (Months)*	3 to 4w	4w	8w	12w	16w	5m	6m	8m	10m	12m	18m	24m	30m	36m	42m	48m
Visit window			+/-1w	+/-1w	+/-1w	+/-2w	+/-2w	+/-1m	+/-1m	+/-1m	+/-2m	+/-2m	+/-2m	+/-2m	+/-2m	+/-2m
Informed Consent	X															
Inclusion/Exclusion criteria	X															
Allocation of study number	X															
Randomisation	X															
Documentation of relapse		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Recent medical/drug history		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event documentation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance check		X	X	X	X											
Physical exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of steroid toxicity		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmoscopy										X		X		X		X
Blood sample for DNA		X														
Achenbach CBC		X			X					X		X		X		X
Peds QL		X			X					X		X		X		X
CHU-9D		X			X					X		X		X		X
	Open label treatment	Randomised phase				Follow-up phase										

* post commencement of prednisolone

4.8 Recruitment

Patients will be approached by their treating consultant paediatrician or paediatric nephrologist.

During the first weeks of treatment, in accordance with routine clinical practice, patients will be treated in an open label manner with prednisolone 60mg/m² daily (maximum dose 80mg). Recruitment and randomisation will take place within this period. The study drug will be sent by Royal Mail Special Delivery in time to allow this to be commenced on day 29. A window of 28 to 31 days is allowed for the start of trial medication and the trial medication can be commenced on the day immediately following the 28th day of daily prednisolone or following a one day interval. Experience from the pilot study showed that this flexibility would make recruitment easier and would enable accommodation of family preferences and unforeseen circumstances without a material impact on the trial interventions.

It is anticipated that the large majority of study patients will be recruited and randomised on or shortly after day 21 of initial open label therapy. This will

- i] allow Principal Investigators a sufficient period of time to recruit the patient
- ii] allow parents adequate time to provide fully informed consent
- iii] allow a sufficient time to have passed to ensure that steroid sensitivity will have been established in the majority (median time to response is 10-14 days).

4.9 Patient and carer information leaflet

The conduct of the trial will be in accordance with the Principles of Good Clinical Practice. The parent's written informed consent to participate in the trial and the child'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.

An information leaflet appropriate for older children and young people who are competent to give informed consent, a leaflet suitable for younger children and a leaflet for parents will be used where appropriate (see Appendices 4-6). The patient's GP will be notified, with the parent's consent.

4.10 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/patient 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/patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The parent/patient 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/patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the parent/patient 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 latest version of the Informed Consent Form. There is also a space for the child to sign (optional) if appropriate. The Investigator or designate must then sign and date the form. A copy of the Informed Consent Form should be given to the

parent/patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient is entered into the trial the patient's trial number should be entered on the Informed Consent Form maintained in the ISF. In addition, if the parent/patient has given explicit consent, a copy of the signed Informed Consent 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 patient'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 Patient Information Sheet and Informed Consent Form. Throughout the trial the parent/patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner.

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

Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log and with the parent's/patient'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.

4.11 Randomisation

Children will be randomised online via a secure 24 hour internet based randomisation service, or by a telephone call to the Birmingham Clinical Trials Unit (BCTU) once informed consent has been obtained. The Investigator must complete the Randomisation Notepad to prepare for, and be able to, randomise. Only delegated staff at the Birmingham Children's Hospital Pharmacy will be able to view the treatment allocation in order to assemble the treatment blister packs. This will be done via a secure login link to the randomisation programme once a patient has been randomised. This method of randomisation will ensure that investigators and the co-ordinating centre are blinded to the patient's treatment allocation to intervention or control treatment. Patients will be randomised between the two treatment groups (standard course therapy or extended course therapy) 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.

Informed consent must be obtained by the local investigator or other qualified local research staff, as detailed in Section 4.10, before randomisation is performed. The investigator should then log into the online randomisation service at <https://www.trials.bham.ac.uk/PREDNOS>, which will ask the investigator to confirm the eligibility criteria. Eligible patients will then be randomised to either standard course therapy or extended course therapy. The patient will also be assigned a unique trial identification number to be used on all trial related material for the patient. 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 patient and inform the investigator of the trial number and ensure that the randomisation information reaches the appropriate study

personnel. A back-up paper randomisation will also be available at the BCTU. The randomisation list will be produced using a block design with the program Sample Size 2.0. 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 ethnicity (South Asian, White, Other) and age (≤ 5 , ≥ 6).

The Local Principal Investigator must fax a signed copy of the Clinical Trial Prescription Form and the Consent/Assent Form(s) (Appendices 7-8) to the Pharmacy at Birmingham Children's Hospital, Fax: 0121 333 9771, once the patient has been randomised, and a PREDNOS trial number has been obtained, to order the PREDNOS trial medication blister pack.

4.12 Trial treatment

Prednisolone and placebo tablets will be manufactured by Essential Nutrition Ltd. Children will be randomised to standard course therapy or to extended course therapy. Children randomised to standard course therapy will receive a combination of prednisolone and placebo tablets from the beginning of week 5 onwards so that they receive the same number of tablets for the same duration as those children receiving extended course therapy. For children unable to swallow tablets whole the prednisolone and placebo tablets can be crushed and a tablet crusher will be supplied with the study medication 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 SOPs. Study drug will be contained within monitored dose packs containing either active drug, a combination of active drug and placebo or placebo tablets alone according to the regimen to which the patient is randomised. The packs, containing the full 3 months supply of the study medication (weeks 5 to 16), will be sent to the patient's home or an alternative address via Royal Mail Special Delivery; as such the patients will be outpatients whilst taking the trial medication. Patients will receive storage information with their medication. If requested, medication can be sent to the local investigator who is then responsible for ensuring the patient gets the trial medication at the correct time.

Compliance with study medication will be assessed at each study visit; the use of monitored dose packs will help facilitate this process.

4.13 Concomitant medications

All other medications are allowed as required through the trial. These should be recorded in the patient CRF.

4.14 Follow-up assessments

All parents and/or patients will be trained to perform early morning urine protein estimation as a part of routine clinical practice. In addition they will be provided with a patient-held record book to enter the results of urine protein testing and the medication administered on a daily basis. Parents will also use this diary to record any intercurrent illness and or consultations with healthcare professionals (GP, nurse, hospital A+E department etc) and details of medicines prescribed or purchased over the counter. This is usual clinical practice and is not considered part of the source records for the study. Information from diaries reported by parents and patients to consultants should be recorded in the medical

record and on the study CRF. The patient's Consultant Paediatrician will ideally perform each review to ensure consistency of reporting.

Clinical trial follow-up assessments will be at weeks 4, 8, 12 and 16 and months 5, 6, 8, 10 and 12, 18, 24, 30, 36, 42 and 48 (see Table 2). All patients will be followed up for at least 24 months and for a variable time period beyond 24 months until 24 months after the last patient is randomised. This is a less onerous visit schedule during year 1 than was used in the pilot study, as feedback from investigators indicated that monthly visits beyond month 6 were unpopular with study participants and beyond the level of routine care normally provided for the large majority of children with NS at this stage post presentation. The scheduled clinical trials follow-up visits have thus been reduced for the convenience of those patients who do not need to attend frequently, but this will have no impact on measurement of trial outcomes, as relapsing patients will still be accurately identified. Follow-up assessments may be made by any appropriately qualified health professionals included on the site delegation log. This may include study nurses or clinical nurse specialists as appropriate. Single assessments after month six (visit 6), except for those performed at 12, 24, 36 and 48 months, may be made in a home visit or over the telephone provided the principal investigator is consulted and agrees that there is no need for the patient to attend hospital. A record of such contacts should be made in the medical record. Following a telephone visit, the next study visit should be conducted at the hospital, so that no two consecutive study visits can be conducted over the telephone.

4.15 Study visits

At each study visit:

Information will be captured regarding recent history of relapse and any treatment for this

A physical examination will be performed, including measurement of height, weight and blood pressure (all omitted for telephone visits, height and weight omitted for home visits)

Scoring of prednisolone adverse effects will be performed by use of a standardised proforma (omitted for telephone visits)

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 the treatment administered

A record will be made of all medicines taken, including those prescribed and those purchased over the counter

At weeks 4, 8, 12 and 16 (visits 1, 2, 3 and 4), a check of trial medication compliance will be made – families will be asked to bring the trial medication along to their child's appointment.

In order to evaluate changes in child behaviour associated with the different prednisolone regimes, the Achenbach Child Behaviour Checklist (ACBC) will be used at the four week visit (visit 1) , when all children will have received one month of daily

prednisolone and at 16 weeks (visit 4) when the randomised treatment is completed. Further assessments will be performed at 12, 24, 36 and 48 months (visits 9, 11, 13 and 15). 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. The ACBC was successfully used in the pilot study and families and children found it an easy tool to use.

At months 1, 4, 12, 24, 36 and 48 information relating to quality of life will also be collected using the CHU-9D and PedsQL questionnaires. These are both brief parent administered questionnaires which will be completed at the time of the study visit.

4.16 Data Collection

The Case Report Form (CRF) will comprise the following forms:

Form	Summary of data recorded	Schedule for submission
Randomisation Notepad	Patient details, confirmation of eligibility and clinical details.	Faxed/sent following randomisation
Follow-up Data Collection Form	Clinical details, primary care visits, hospital admissions, hospital A&E visits, hospital outpatient visits, medication, adverse effects, patient withdrawal.	Faxed/sent/submitted online after each follow-up assessment time point (week 4, 8, 12 and 16 and month 5, 6, 8, 10, 12, 18, 24, 30, 36, 42 and 48)
Serious Adverse Event Form	Details of any SAE occurring during trial treatment or up to 3 months following trial treatment	Faxed within 24hrs of research staff becoming aware of event.
Child Health Utility (CHU) -9D	Child Quality of Life (parent rated)	Faxed/sent after follow-up assessment at week 4 and 16, and month 12, 24, 36 and 48.
PedsQL	Child Quality of Life (parent rated)	Faxed/sent after follow-up assessment at week 4 and 16, and month 12, 24, 36 and 48.
Achenbach	Child behaviour (parent rated)	Faxed/sent after follow-up assessment at week 4 and 16, and month 12, 24, 36 and 48.

When available, CRFs can be entered online at <http://www.bctu.bham.ac.uk/PREDNOS>. Authorised staff at sites will require an individual secure login username and password to access this online data entry system. Paper CRFs must be completed, signed/dated and returned to the Study Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above. The exception to this will be the SAE Form which must be co-signed by the Investigator.

Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form 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 form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

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

The completed originals should be sent to the Trials Office and a copy filed in the Investigator Site File

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.

4.17 Outcome Measures

4.17.1 Primary study endpoint:

- Time to first relapse. Relapse of proteinuria is defined by Albustix positive proteinuria (+++ or greater) for 3 consecutive days or the presence of generalised oedema plus 3+ proteinuria.

4.17.2 Secondary endpoints/ outcome measures:

- Rate of relapse
- Incidence of frequently relapsing steroid sensitive nephrotic syndrome (defined as 2 relapses or more in the first six months following presentation or 4 relapses within any 12 month period)
- Incidence of steroid dependent nephrotic syndrome (defined as relapses on or within 14 days of completion of steroid therapy) nephrotic syndrome
- Incidence of use of second line immunosuppressive agents, including levamisole, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil and rituximab
- Rate of serious adverse events
- Rate of adverse events
- Incidence of behavioural change (as assessed by the Achenbach child behaviour checklist)
- Cost per relapse of proteinuria
- Cost per QALY gained

4.18 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 child 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 as described above.
- 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; where this is significant and persistent plasma glucose will be measured in keeping with routine clinical practice.
- ix. Ophthalmological examination annually to look for evidence of cataract formation.
- x. The development of significant bacterial, viral and fungal infections will be documented.
- xi. Use of varicella prophylaxis (zoster immune globulin or antiviral therapy) will be recorded.
- xii. We will prospectively collect information regarding all episodes of consultation with General Practitioners or hospital medical teams, including data on treatment 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 ensure that the local Principal Investigator has assigned causality and expectedness to the SAE before reporting.

4.19 Stopping rules and unblinding

There may be medical emergencies where it is necessary for a patient's treatment to be unblinded. There is no need for unblinding in the first four weeks of routine clinical treatment, as all patients are receiving comparable doses of prednisolone in an open fashion.

Between week 5 and week 16, unblinding should only occur when there is a clinical need to know whether the patient is receiving prednisolone and, if so, at what dose, 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.

There should be no need for unblinding after patients have finished the study medication, 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 this period should be referred to the Chief Investigators.

For a request for unblinding which does not fall under the above situations the pharmacist will ask the local PI to contact one of the trial investigators (contact details below). If for any reason they are unable to contact the investigators, the pharmacist will attempt to do this on their behalf. The pharmacist will await outcome of this contact before unblinding the patient. In an emergency the pharmacist has the discretion to break the code without input from the investigators.

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

Patients who cease study medication will be followed up for the entire duration of the study; the only exception to this being in those where there is withdrawal of consent by the patient/parent. A record will be made of any patients who cease study medication and the reason(s) for this.

4.20 Blood sample collection for DNA isolation and substudies

4.20.1 Genome-wide association study of steroid sensitive nephrotic syndrome

This substudy 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 part of University College, London). The aim of the study is to identify any genetic mutations which may be associated with childhood steroid sensitive nephrotic syndrome. The identification of a genetic mutation associated with the development of steroid sensitive nephrotic syndrome would improve 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.

4.20.2 Investigation of DNA methylation

This substudy investigating DNA methylation will be conducted in collaboration with Dr Rachel Lennon and Professor David Ray of the University of Manchester.

Children treated with high dose steroids have a very variable response to treatment and we hypothesise that this is related to differences in DNA methylation. This study provides a unique opportunity to investigate the effects of standard and extended course steroid treatment on target gene methylation, which is a permanent switch altering gene function. Once the switch has occurred cells continue to respond as though treatment is ongoing. The methylation profile of extracted DNA will be analysed and standard and extended course samples will be compared. Together with clinical course information, we will correlate DNA methylation state to outcome. If DNA methylation profiles associates with clinical course, it may be possible to personalise steroid treatment for individuals.

Blood sampling

As part of the consent and assent process, permission will be obtained to collect a single 10ml blood sample for DNA isolation at any time during the patient's follow-up within the trial, preferably at the time of routine venepuncture for clinical purposes. Blood will be collected into two 5ml EDTA containing blood tubes which will be provided free of charge

by the substudy investigators to all study sites. Samples will be labelled only with the patient's study number, thus maintaining strict anonymity. Once collected, study sites will mail both blood samples to Dr Bockenbauer's laboratory at the Institute of Child Health, London using pre-paid addressed packaging which will be provided for all study sites by Dr Bockenbauer. DNA will be isolated from the blood samples in his laboratory using standard techniques. The DNA sample obtained will be split into two equal portions; one will be retained in Dr Bockenbauer's laboratory and the other transported by mail in batches to Professor Ray's laboratory for the DNA methylation studies.

Following completion of the above studies, any remaining DNA samples will be retained in the laboratories of Dr Bockenbauer/Prof Kleta in London and/or Dr Lennon/Professor Ray in Manchester for use in future research projects investigating genetic factors and disease mechanisms in steroid sensitive nephrotic syndrome which may arise as a result of this work. Any such studies on these samples would require Research Ethics Committee approval.

4.21 Sample size

A total of 236 children will be recruited into the study (118 in each study arm)

The primary analysis will be based on a log-rank test of time to relapse. It is anticipated that the relapse rate in the control group will be 60% at 1 year. To detect an absolute difference of 20% in relapse rate, from 60% to 40% at 1 year, with 80% power at $2p=0.05$ will require 100 relapses. Given the expected relapse rates we anticipate needing 200 patients in total. If allow for 10% dropout, then this will require recruitment of 224 patients (112 per arm). As dropout of 15% has been observed during the study the sample size has been increased to 236 children (118 per arm).

An audit undertaken by the BAPN⁸ on the management of childhood NS in the UK identified and collected data from 188 out of 238 newly diagnosed patients over a 14 month period, reflecting a great willingness amongst Paediatricians and Paediatric Nephrologists to cooperate in research in the field of NS. The numbers necessitate the trial being performed on a large scale national basis and we are pleased to have the support of the MCRN and the BAPN. Recruitment rates in the pilot trial have provided evidence that it is practical to commence to a large scale multi-centre UK national trial. At present it is anticipated that the recruitment target is attainable within three years without having the need to resort to international resources. The pilot trial recruited a total of 50 evaluable patients within a 23 month period at a total of only 18 sites, providing evidence that it is feasible to recruit this patient population to this trial design.

4.22 Statistical Analysis

The primary outcome measure is time to relapse. Time to first relapse will be assessed across the two treatment arms and compared using the log-rank test. If important prognostic factors are unbalanced between the two arms at baseline, then a secondary analysis using a Cox proportional hazards model will be performed.

The secondary outcomes include both continuous and categorical data items. Continuous outcomes (e.g. Achenbach scores) will be analysed using repeated measures methods using the data available at each time point, including the baseline scores as covariates in the model. Separate analyses will also be carried out for each time point to allow for the possibility that adverse effects (as measured by the Achenbach) have differing short and

long term responses to the treatment. Dichotomous outcomes or count data will be analysed using logistic or Poisson regression, as appropriate.

Analysis will be of all randomised patients using intention to treat, except for those who fail to respond to prednisolone following randomisation. Exclusion of these patients will result in no bias as (1) these dropouts occur prior to the commencement of randomised treatment, and (2) clinicians will be unaware of the treatment assigned to their patients. It is anticipated that rates of missing data will be low, and there will be no need for imputation. A full statistical plan will be written for the trial, and any deviations from this plan will be described in the final report.

Interim analyses of efficacy and safety will be monitored by a data monitoring and ethics committee (DMEC) at intervals determined by the DMEC. The Haybittle-Peto approach will be used, whereby all interim analyses will use a difference of 3 standard errors (approximately $p=0.002$) as a stopping guideline.

There are 2 planned subgroup analyses – ethnicity (South Asian, White, Other) and age (≤ 5 , $>=6$). In order to ensure a reasonable balance of patients within each subgroup, the randomisation will be minimised by each of these variables.

4.23 Health Economic analysis

The economic evaluation will take the form of a cost-effectiveness analysis within a decision-tree framework based on a primary clinical outcome of cost per episode of '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. The model will make a direct comparison between the strategy of administering standard therapy (prednisolone daily for 4 weeks with reduced dose alternate day prednisolone over a further 4 weeks) and a strategy of administering extended course therapy (prednisolone daily for 4 weeks with gradually reducing alternate day prednisolone over 12 weeks).

The base case economic evaluation will adopt the NHS perspective. NHS costs will include:

- A. Treatment costs: medicines, management, adverse-effects, treatment complications;
- B. Consultation and follow-up costs: routine tests such as blood tests and urinalysis, number of outpatient visits, inpatient visits, GP visits.
- C. Longer term treatment costs (care for long-term adverse effects).

Doctors will record information regarding intercurrent illness, visits to the child's GP, hospital (as an outpatient or inpatient) and medicines supplied in the follow-up data collection form which is provided for them. This information will be collected at the time of study visits.

Resource use information will be collected as part of the trial using the follow-up data collection form and unit cost data will be derived from sources such as the British National Formulary (BNF), the National Schedule for Reference Costs and the Unit Costs of Health and Social Care (PSSRU).

Two different methods will be used to estimate utility data for the two broad groups into which both our intervention and control groups will be divided i.e. children aged 5 years and above and for those aged below 5 years. For the former, parents will complete the proxy version of the CHU-9D and the resulting descriptive profiles will be converted into

utility values using conventional methods. For the latter, CHU-9D utility values will be predicted from PedsQL scores using regression mapping algorithms. These algorithms will be determined by modelling the relationship between the CHU-9D and PedsQL scores for children for whom both will have been collected (i.e. those aged 5 years and above). 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 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 (standard therapy vs. extended course 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.

Figure 2: Illustrative decision-analytic model

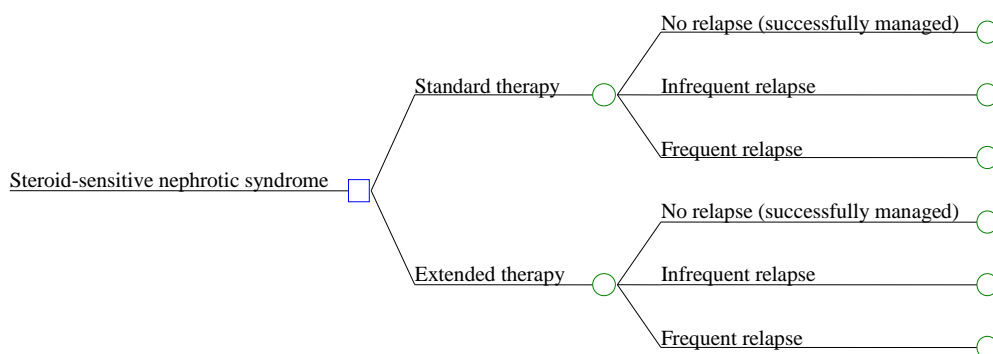


Figure 3 outlines the full economic analysis with respect to the instruments being administered and the data being collected throughout the time period of the trial.

Months	1	4	12	Every 12 months thereafter
NHS Perspective	PedsQL ACBC CHU-9D (proxy)	PedsQL ACBC CHU-9D (proxy)	PedsQL ACBC CHU-9D (proxy)	PedsQL ACBC CHU-9D (proxy)

4.24 Vaccination

Where the child is due for routine vaccination, or specialized 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.

Children 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 patient within the trial please seek the advice of an immunologist or specialist within the field.

5. SAFETY ASSESSMENT AND REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed below. The Investigator should 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 most recent updated SmPC. Up-to-date SmPCs of licensed products are available at <http://emc.medicines.org.uk/>.

5.1 Definitions of Types of Adverse Events

Within the PREDNOS trial the steroid prednisolone is defined as an Investigational Medicinal Product (IMP).

5.2 Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or clinical trial patient 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 current Summary of Product Characteristics (SmPC; for licensed drugs) or Investigators Brochure (IB; for an unapproved IMP or licensed IMP for non-licensed use). Information on the current expected events is also given in Appendix 2.

As the safety profiles of the Investigational Medicinal Product used in this trial is well characterised, only Adverse Reactions (ARs) experienced during treatment will be reported.

The following are not AEs:

- 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).

5.3 Adverse Reactions (ARs)

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.

5.4 Serious Adverse Events (SAEs)

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 patient 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.

** 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 should report AEs that meet the definition of an SAE and are not excluded from the reporting process as described below.

Expected SAEs are those listed in the current SmPC or IB for the study drugs. Please always use the most recent updated SmPC. Up-to-date SmPCs of licensed products are available at <http://emc.medicines.org.uk/>. Information on the current expected events is also given in Appendix 2.

For this reason the following SAEs do not require expedited (immediate) reporting by the site and are not regarded as unexpected for the purpose of this trial:

Events NOT considered to be SAEs are 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.

Note: Death from any cause should be reported on an SAE form and returned to the PREDNOS Trial Office at the BCTU.

5.5 Serious Adverse Reactions (SARs)

An SAR is an SAE judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IMP. The expression “reasonable causal relationship” means in general that there is evidence or argument to suggest a causal relationship. Factors to consider when assessing causality of SARs are i) the nature of the reaction; ii) timing of the reaction; and iii) the relationship to the dose.

5.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR is an SAR, which is of a type or severity which is NOT consistent with the up-to-date product information in the SmPC or IB. Information on the current expected events is given in Appendix 2. Please always use the most recent updated SmPC. Up-to-date SmPCs of licensed products are available at <http://emc.medicines.org.uk/>.

Details of all SAEs (except those listed above as being excluded) will be documented and reported from the date of commencement of protocol defined treatment until three months after the administration of the last treatment.

5.7 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.

5.8 Reporting all Types of Adverse Events

5.8.1 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 data collection form. The BCTU will provide details of all adverse events to the Data Monitoring and Ethics Committee (DMEC) for their review on an annual basis.

5.8.2 Reporting Serious Adverse Events/Reactions

All SAEs 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 ensure that the local Principal Investigator has assigned causality and expectedness to the SAE before reporting.

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*

- Whether the event would be considered expected or unexpected* (refer to the most recent and relevant SmPC or IB).

*Assessment of causality and expectedness **must be made by a doctor**. If a doctor is unavailable, initial reports without causality and expectedness 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.

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.

5.8.3 Reporting SUSARs

SAEs classed by the local investigator as both suspected to be related to the trial drugs and unexpected are SUSARs, and are subject to expedited reporting. The investigator should complete a SAE form, and fax to the BCTU within 24 hours of the research staff becoming aware of the event.

The Chief Investigator (or nominated individual) will undertake urgent review of SUSARs within 24 hours of the event being reported to the BCTU and may request further information immediately from the patient's clinical team. The Chief Investigator will not overrule the causality, expectedness or seriousness assessment given by the local investigator but may comment on these and can upgrade if deemed appropriate

The BCTU will report all SUSARs to the MHRA and the MREC. If the SUSAR resulted in death or was life-threatening this will be done within 7 days of the initial report being received, or within 15 days for any other SUSAR.

If information is incomplete at the time of initial reporting, the BCTU will request follow-up information, including information for analysis of causality, from the local investigator and will send the follow-up information to the MHRA and MREC within an additional 8 days for fatal or life-threatening SUSARs, and as soon as possible for any others.

5.9 Pharmacovigilance Responsibilities

Local Investigator:

- Medical judgement in assigning seriousness, expectedness 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 report all adverse drug reactions suspected to be related to other licensed drugs used in standard care using the yellow card system.
- 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 review all events assessed as SAEs or SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and Chief

Investigator review with regards to SUSAR status, local assessment will not be overruled, but 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 MREC within the required timelines.
- To notify Investigators of all SUSARs which compromise patient safety.
- To prepare annual safety reports to MHRA, MREC, Trial Steering Committee (TSC), Trial Sponsor and Novartis.
- To prepare SAE reports for the DMEC at intervals to be decided by the DMEC.

Trial Steering Committee:

- To periodically review blinded safety data and 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.

5.10 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 licensing authority 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 will employ central statistical monitoring of data. This monitoring process will be applied by the Birmingham Clinical Trials Unit. 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 Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be sent missing data requests and asked for clarification of 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 Research Ethics Committee (REC) and the Medicines for Healthcare products Regulatory Agency (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. Additional sites will undergo random on-site monitoring on a periodic basis. 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 Birmingham Clinical Trial Unit.

The trial is considered to be low risk, all investigators and staff will follow Good Clinical Practice 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 Good Clinical Practice and all applicable regulatory requirements. Participating sites will be provided with SOPs detailing how to conduct the trial and the co-ordinating centre will check that the PI understands these prior to commencement of recruitment at the site. Data will be monitored centrally by the trial co-ordination centre.

7.2 Data and Safety Monitoring Plan

An independent Data Monitoring Committee (DMC) will be established for this trial and will include at least one member from each of the following designations: a statistician, an expert in childhood nephrotic syndrome and an expert in trial methodology. The DMC will meet annually to review all collected data and may meet more frequently if required after analysis of the available data. The DMC will advise the Trial Management Committee and the independent Trial Steering Committee on the safety of continuing this clinical trial.

All unexpected serious adverse events 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 within 24 hours of knowledge of their occurrence by local investigators. All data regarding the occurrence of adverse events will be made available to the DMC 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. Both treatments in the trial are used in current clinical practice and children participating in the trial will face minimal additional risk. Informed consent will be sought from parents and children can also sign this consent form (optional) as appropriate. Age appropriate patient information leaflets for children and young people will be provided.

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 will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trials Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. 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, Edgbaston, Birmingham B15 2TT

Telephone 0121 415 9131

Fax 0121 415 9135

Email: PREDNOS-trial@contacts.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.

The Clinical Trial Prescription and Parent Consent Form, which will be sent to the Birmingham Children's Hospital which 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.

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 Birmingham Clinical Trials Unit 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 initials, date of birth and hospital number will be collected at trial entry to assist with long-term follow-up. 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 make up the treatment blister packs and send these directly to the parent's home address. Patients will be identified using only their unique trial number, date of birth, hospital number and initials on the Case Report Form and correspondence between the Trials Office and the participating site. 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. This will be used to perform in-house monitoring of the consent process. 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 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.

Participants will be informed that their trial data and information will be securely stored at the trial office at the Birmingham Clinical Trials Unit, 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 Birmingham Clinical Trials Unit 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 stored for at least 5 years (but ideally not less than 15 years). 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 was developed by members of the PREDNOS Trial Management Group and is funded by a grant from National Institute for Health Research Health Technology Assessment programme. The University of Birmingham and Central Manchester University Hospitals NHS Foundation Trust 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 conduct of the trial will be according to the Medicines for Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments and the principles of the International Committee on Harmonisation Good Clinical Practice Guidelines.

11.1 Sponsor

The University of Birmingham and Central Manchester University Hospitals NHS Foundation Trust will share responsibilities for co-sponsorship of the trial. The trial is being coordinated by the Birmingham Clinical Trials Unit 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, Good Clinical Practice, confidentiality and publication.

11.2 Trial Organisation

Chief Investigator

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

Co-Chief Investigator

Dr Richard Trompeter, Great Ormond Street Hospital, London

Co-Investigators

Dr Carole Cummins, Prof Keith Wheatley, Dr Emma Frew, Dr Billingsley Kaambwa and Miss Natalie Ives

University of Birmingham

Principal Investigator

Each centre should nominate one person to act as the Local Principal Investigator, who will be responsible for obtaining local R&D Department approval at their centre. 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 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 will be submitted for adoption by the Medicines for Children Research Network. 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 depends on the collaboration of a large number of staff including nephrologists and nurses. For this reason, chief credit for the results of this pilot study will be given not to the central organisers, but to all those who have collaborated in the study. The Writing Committee will approve all publications using PREDNOS data and the authorship. The Writing Committee will be composed of the PI's, 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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8. Evans JHC, Long E. A national audit of nephrotic syndrome: The initial course of prednisolone and outcome. Abstract. *Ped Nephrol* 1998;**12(7)**:C154