

# **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 pilot study**

**Short Title: Long-term tapering or standard steroids for nephrotic syndrome**

EudraCT number – 2004-001813-33

ISRCTN –

Sponsor's Project number – 03/NU/13

Dr Richard Trompeter and Dr Nicholas Webb  
on behalf of  
the Royal College of Paediatrics and Child Health and  
British Association of Paediatric Nephrology

Dr Carole Cummins,  
Institute of Child Health, University of Birmingham

**Protocol Version 1.2**

**Date 28<sup>th</sup> March 2006**

**Funding Body**

Kidney Research UK

1.	SUMMARY .....	3
2.	GENERAL INFORMATION .....	4
2.1	Sponsor responsibilities.....	4
2.2	Name and address of trial monitor and co-ordinating centre .....	4
2.3	Trial Steering Committee .....	4
2.4	Data Monitoring Committee.....	4
2.5	Sponsor’s medical expert for the trial .....	5
2.6	Person entitled to sign protocol amendments.....	5
3.	BACKGROUND.....	5
3.1	Treatment .....	5
3.2	Research question.....	6
3.3	Trial objectives.....	6
3.4	Investigational medicinal product.....	6
3.5	Name of supplier .....	6
3.6	Summary of known and potential risks and benefits.....	6
3.7	Trial conduct.....	6
4.	TRIAL DESIGN.....	7
4.1	Introduction.....	7
4.2	Inclusion criteria.....	7
4.3	Exclusion criteria .....	8
4.4	The Research Setting.....	8
4.5	Recruitment .....	9
4.6	Patient and carer information leaflet.....	10
4.7	Randomisation.....	10
4.8	Trial treatment .....	10
4.9	Follow-up and outcome measures.....	10
4.10	Stopping rules and unblinding .....	11
4.11	Sample size .....	11
4.12	Statistical Analysis.....	11
5.	PHARMACOVIGILANCE.....	12
6.	DIRECT ACCESS TO SOURCE DATA/DOCUMENTS: AUDITING, MONITORING AND INSPECTION .....	12
7.	QUALITY CONTROL AND QUALITY ASSURANCE.....	12
8.	ETHICAL CONSIDERATIONS .....	13
9.	DATA HANDLING AND RECORD KEEPING .....	13
10.	FINANCING AND INSURANCE .....	13
11.	REFERENCES.....	13

## 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 therapy<sup>1,2</sup>. 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 side effects or the prescription of more potent immunosuppressive therapies including alkylating agents to control the disease<sup>3</sup>.

There is emerging evidence from a Cochrane review<sup>8</sup> 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 side-effects, making interpretation of the impact of increased duration of steroid therapy on side-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 required. We propose to carry out a pilot study for such a trial and have developed a draft protocol with advice from Dr Colin Baigent of the CTSU, Oxford University and Prof Keith Wheatley, BCTU, Birmingham University. The information from this study will enable the fine-tuning of the definitive study's design and will provide evidence of successful collaboration, thus enhancing the prospects for obtaining funding for a definitive trial.

We therefore propose comparing a long-term (four months) tapering prednisolone regimen with the standard two months regimen as originally proposed by the International Study of Kidney Disease in Children (ISKDC).

In order to prepare for a large-scale national or international multi-centre randomised double-blind placebo-controlled trial, a pilot study is needed. The pilot study will provide data to support the trial design and power calculations. More specifically it will:

- Provide information on recruitment rates.
- Provide further evidence on the incidence of trial outcomes that can be used to inform 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.

The pilot study will also contribute patients to the definitive study and provide "proof of principle" on successful recruitment and collaboration.

The long term tapering regime may result in less frequent relapses, but may also result in an important increase in side effects of prednisolone treatment.

## **2. GENERAL INFORMATION**

### **2.1 Sponsor responsibilities**

The person allocated responsibility to carry out the functions of the sponsor is:

Miss Emma Pendleton  
Head of Research and Development  
Institute of Child Health  
London

### **2.2 Name and address of trial monitor and co-ordinating centre**

Dr Rachel Cook  
Nephrotic Syndrome Trial Co-ordinator  
Institute of Child Health  
Whittall Street  
Birmingham  
B4 6NH

### **2.3 Trial Steering Committee**

Membership of the Trial Steering Committee as of 28<sup>th</sup> March 2006:

Dr Richard Trompeter (Consultant Paediatric Nephrologist)  
Institute of Child Health & Great Ormond Street Hospital  
London

Dr Nicholas Webb (Consultant Paediatric Nephrologist)  
Royal Manchester Children's Hospital  
Manchester

Dr Carole Cummins (Senior Lecturer, Paediatric Clinical Trials)  
Institute of Child Health  
Birmingham

### **2.4 Data Monitoring Committee**

Membership of Data Monitoring Committee at 27<sup>th</sup> January 2004:

Professor Adrian White  
Head of Nephro-Urology

Institute of Child Health  
London

Dr Martin Landray  
Clinical Trials Service Unit  
University of Oxford

### **2.5 Sponsor's medical expert for the trial**

Dr Richard Trompeter (Consultant Paediatric Nephrologist)  
Nephro-Urology Unit  
Institute of Child Health & Great Ormond Street Hospital  
London  
WC1 3JH  
Tel: 0207 405 9200 ext 5976

### **2.6 Person entitled to sign protocol amendments**

Dr Richard Trompeter (Consultant Paediatric Nephrologist)

## **3. BACKGROUND**

### **3.1 Treatment**

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 side-effects develop. The first standardised corticosteroid treatment regimen was introduced by the ISKDC in the 1960s and consisted of prednisone 60mg/m<sup>2</sup> given daily for 4 weeks followed by 40mg/m<sup>2</sup> on 3 consecutive days out of seven for a total of 4 weeks<sup>4</sup>. Many centres made a minor modification whereby 40mg/m<sup>2</sup> 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<sup>5,6</sup>.

A recent meta-analysis has suggested that children who receive 3 months or more steroid therapy at disease presentation have a significantly higher relapse-free rate at 12 months post-presentation than those who receive the standard regimen<sup>7</sup>, but there were concerns over trial quality.

There is emerging evidence from a Cochrane review<sup>8</sup> 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 side-effects, making interpretation of the impact of increased duration of steroid therapy on side-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 group comment 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 side-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. We propose to carry out a pilot study for such a trial and have developed a draft protocol with advice from Dr Colin Baigent of the CTSU, Oxford University and Prof Keith Wheatley, BCTU, Birmingham University. The information from this study will enable the fine-tuning of the definitive study's design and will provide evidence of successful collaboration, thus enhancing the prospects for obtaining funding for a definitive trial.

### **3.2 Research question**

We therefore propose comparing a long-term (four months) tapering prednisolone regimen with the standard two months regimen as originally proposed by the International Study of Kidney Disease in Children (ISKDC).

### **3.3 Trial objectives**

In order to prepare for a large-scale national or international multi-centre randomised double-blind placebo-controlled trial, a pilot study is needed. The pilot study will provide data to support the trial design and power calculations. More specifically it will:

- Provide information on recruitment rates.
- Provide further evidence on the incidence of trial outcomes that can be used to inform 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.

The pilot study will also contribute patients to the definitive study and provide "proof of principle" on successful recruitment and collaboration.

The long term tapering regime may result in less frequent relapses, but may also result in an important increase in side effects of prednisolone treatment

### **3.4 Investigational medicinal product**

Prednisolone is a licensed corticosteroid immunosuppressant.

### **3.5 Name of supplier**

Essential Nutrition Ltd.

### **3.6 Summary of known and potential risks and benefits**

See Summary of Product Characteristics for generic formulation of prednisolone (Appendix A).

IMPs will only be used for trial subjects.

### **3.7 Trial conduct**

This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

## 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 therapy is prednisolone 60mg/m<sup>2</sup>/day for four weeks with a reduced dose over a further four weeks (Table 1).

Alternative therapy: The proposed alternative therapy also has prednisolone 60mg/m<sup>2</sup>/day for four weeks, but the prednisolone is reduced more gradually over a further twelve weeks (Table 1).

The study will be double blinded. Study drug dispensed as 5mg tablets will be contained in monitored dose packs containing either active drug or placebo tablets according to the regimen to which the patient is randomised. Only 5mg tablets and no 25mg, 50mg or 1 mg tablets will be used in the study. All doses will be given as a single dose with breakfast. During the first weeks of treatment, subjects will be treated identically with prednisolone 60mg/m<sup>2</sup> daily (maximum dose 80mg). Recruitment and randomisation will take place within this period. Patients will then receive a combination of active drug and placebo to allow different doses of prednisolone to be prescribed in a blinded manner (Figure 1).

At the outset of the study, we shall ask all centres signed up to the study to standardise the prednisolone preparation, which they use in all newly presenting nephrotics. We shall recommend that non-enteric coated prednisolone tablets should be used, these being crushed for smaller children unable to swallow tablets whole. Soluble and enteric-coated prednisolone should not be used. Children in both treatment arms will receive the same number of tablets at any time-point in the study.

**Table 1: Standard therapy and long term tapering therapy**

Standard regimen		Long-term tapering regimen	
Time	Prednisolone dose	Time	Prednisolone dose
Week 0-4	60mg/m <sup>2</sup> /day (max 80mg)	Week 0-4	60mg/m <sup>2</sup> /day (max 80mg)
Week 5-8	40mg/m <sup>2</sup> on alternate days	Week 5-6	60mg/m <sup>2</sup> on alternate days
		Week 7-8	50mg/m <sup>2</sup> on alternate days
		Week 9-10	40mg/m <sup>2</sup> on alternate days
		Week 11-12	30mg/m <sup>2</sup> on alternate days
		Week 13-14	20mg/m <sup>2</sup> on alternate days
		Week 15-16	10mg/m <sup>2</sup> on alternate days

Formatted: Bullets and Numbering

Formatted: Indent: Left: 13.5 pt

We shall use a pack containing patient diaries/standard urinalysis sticks which shall be available in all hospitals to make the job of the recruiting district paediatrician as uncomplicated as possible, thus encouraging centre participation in the study and patient recruitment.

### 4.2 Inclusion criteria

Children presenting with the first episode of steroid sensitive NS who meet the following criteria:

- Urine albumin: creatinine ratio > 200mg/mmol, determined quantitatively on a early morning urine sample
- Hypoalbuminemia < 25g/L
- Age over 1 year and less than 15 years at the time of diagnosis.
- No prior therapy with steroids or cytotoxic agents
- No evidence of underlying systemic disorder or exposure to agents known to be associated with newly presenting steroid sensitive nephrotic syndrome (NS)

#### **4.3 Exclusion criteria**

- Children who are resistant to steroid therapy.(No clinical response after 28 days of daily prednisolone at 60mg/m<sup>2</sup>/day)
- Children with histological changes other than minimal lesion glomerulonephritis
- Patients with poor compliance.

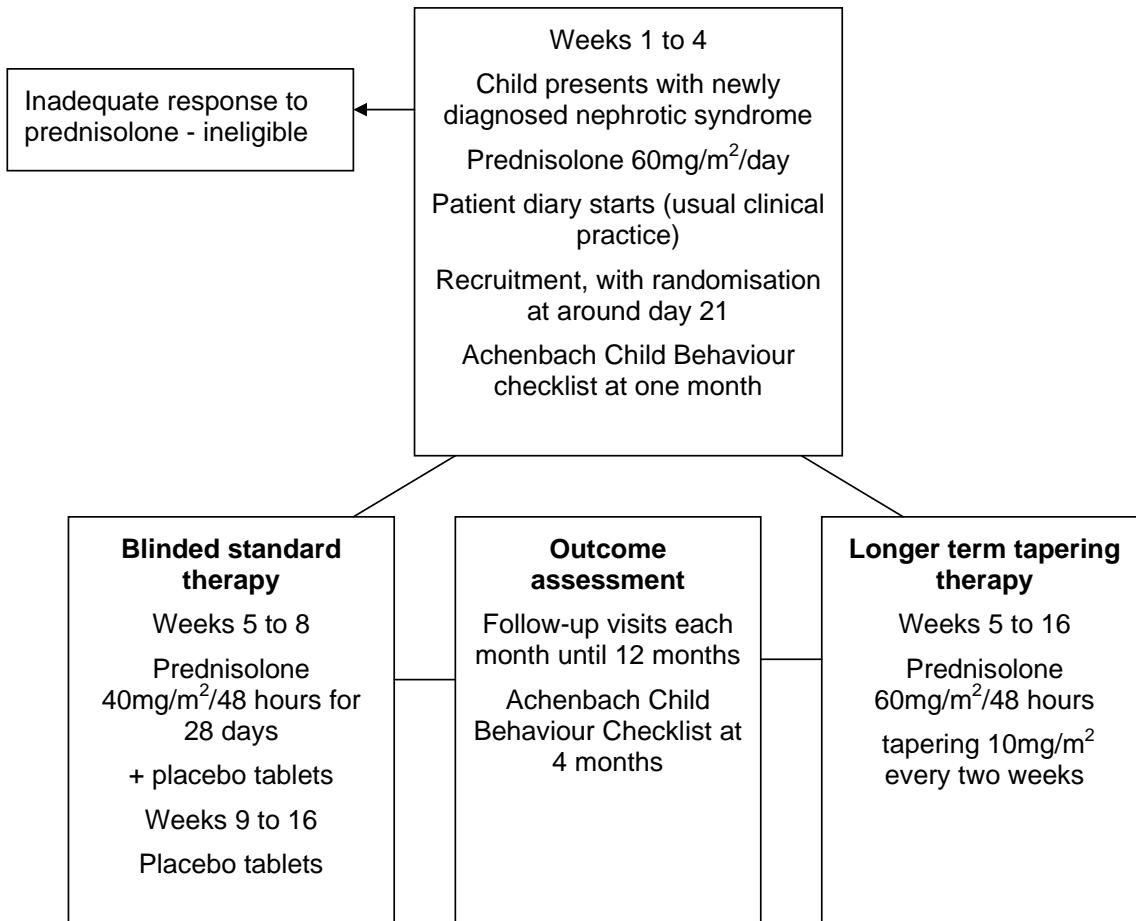
#### **4.4 The Research Setting**

Patients will generally be recruited, randomised and followed-up in district general hospitals (it is here that the large majority of children present, and referral to tertiary paediatric nephrology units does not generally occur in the presenting episode unless the clinical course is atypical or complicated). A small number of centres may request that follow-up take place in the regional paediatric nephrology centre.

The paediatric nephrologists in the tertiary centres will act in an advisory role and will be responsible for advertising the study within their own region: this might be through a lecture/seminar or by word of mouth.

We aim to involve all regions of the UK as this will test the true feasibility of a larger national/international study. Parents of children presenting with the first episode of NS to all UK paediatric units will be invited to participate. There are 12 paediatric nephrology centres in the UK, including the Institute of Child Health in Birmingham, which have given unequivocal support to the study

**Figure 1 Study flow chart**



**4.5 Recruitment**

Patients will be approached by their own consultant paediatrician or paediatric nephrologist. The paediatric nephrologists in the tertiary centres will act in an advisory role and will be responsible for advertising the study to paediatricians within their own region: this might be through a lecture/seminar or by word of mouth.

During the first weeks of treatment, patients will be treated identically with prednisolone 60mg/m<sup>2</sup> daily (maximum dose 80mg). Recruitment and randomisation will take place within this period. The study drug will be sent by post in time to allow this to be commenced on day 28. Patients should be randomised around day 21 of therapy. This will

- i] give district paediatricians a significant period of time to recruit the patient
- ii] give parents adequate time to allow 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).

#### **4.6 Patient and carer information leaflet**

The conduct of the trial will be in accordance with the Medical Research Council (MRC) Guidelines for Good Clinical Practice 1998 and any subsequent amendments. The parent's written informed consent to participate in the trial and the child's informed consent or 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. The patient's GP will be notified, with the parent's consent.

#### **4.7 Randomisation**

Children with newly presenting steroid sensitive nephrotic syndrome (NS) will be randomised by a telephone call or fax to the Institute of Child Health Birmingham University once informed consent has been obtained. This method of randomisation will ensure that investigators are blind to the patient's allocation to intervention or control treatment. The randomisation list will be produced using a block design with the program SampleSize 2.0.

#### **4.8 Trial treatment**

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

Children will be randomised to standard therapy or to longer term tapering therapy. Children randomised to standard therapy will have prednisolone and placebo tablets so that they receive the same number of tablets for the same duration as children receiving longer term therapy

The pharmacy at Birmingham Children's Hospital NHS Trust will dispense the drugs and be responsible for drug accountability in line with their SOPs. Study drug will be contained in monitored dose packs containing either active drug or active drug and placebo tablets according to the regimen to which the patient is randomised. The packs will be sent to the patients via Royal Mail Special Delivery at their home; as such the patients will be out patients whilst taking the trial medication. A DDX certificate has been applied for in preparation for an application for a Clinical Trials Authorisation to be made to the Medicines and Healthcare Regulatory Authority before the implementation of the E.U. Clinical Trials Directive.

#### **4.9 Follow-up and outcome measures**

All parents and/or patients will be trained to perform early morning urine protein estimation as a part of routine 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. All patients will be reviewed monthly throughout the study period. The patient's Consultant Paediatrician will ideally perform each review to ensure consistency of reporting.

Patients will be seen monthly at their district general hospital (in keeping with standard clinical practice) for a total of 12 months in the pilot study, with consent obtained for further follow-up if the substantive trial goes ahead. We will use a non-carbon copy single entry study visit form: one copy will be retained in the notes and will serve as the record of the in-patient visit, the other being sent to the study co-ordinator in Birmingham by fax/mail. The study co-ordinator will be responsible for liaising with participating centres, reminding them of study visit timings and chasing up doctors and parents where data are not submitted.

Patients will keep a diary (as is standard clinical practice) outlining urine results, therapy administered etc. We will provide this so that a standard format is used and to assist the paediatrician with recruitment. Information from diaries reported by parents and patients to consultants should be recorded in the medical record and on the study CRF.

In order to evaluate changes in child behaviour associated with the different prednisolone regimes, the Achenbach Behavioural Checklist will be used at one month (baseline data after all have received one month of 60mg/m<sup>2</sup>) and at 4 months when the longer treatment arm will have finished treatment and the standard treatment arm will have been off therapy for 2 months.

The study will incorporate a system for reporting serious adverse events, with reports to be sent to the clinical principal investigators (NW and RT).

Pilot trial endpoints: Primary: Relapse of proteinuria as defined by Albustix positive proteinuria (++ or greater) for 3 consecutive days.

Secondary endpoints/ outcome measures: Frequently relapsing and steroid dependent disease, time to relapse, serious adverse events and the use of other immunomodulatory or immunosuppressive agents at the end of the study period. Achenbach child behaviour checklist.

#### **4.10 Stopping rules and unblinding**

A patient at their consultant's discretion may need to cease the study drug in event of a relapse of nephrotic syndrome or adverse event. In these circumstances, the consultant may need to know what the study medication was at that point. A code-break will be available via the BCH Pharmacy. Patients who cease study medication will still be followed up in line with the protocol unless consent is withdrawn.

A record will be made of any patients who withdraw from the study and of the reasons for withdrawal.

#### **4.11 Sample size**

50 patients will be recruited in the pilot study. The numbers necessitate the trial being performed on a national basis and we are pleased to have the support of the RCPCH and the BAPN. An audit undertaken by the BAPN<sup>9</sup> 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. Recruitment rates in the pilot trial will help determine the timescale of recruitment and whether international collaboration should be sought in the definitive study.

#### **4.12 Statistical Analysis**

Descriptive statistical analysis will be used to inform the design of the definitive trial. A preliminary power calculation for a substantive trial based on a 40% relapse free rate at 12 months with the standard regimen and 60% with the intervention suggested that with 80% power and statistical significance set at 5%, 95 patients would be required in each arm. A more modest difference would however be of clinical significance, and time to relapse would be the preferred outcome to detect this. Further calculations will be carried out once the pilot data are available. Recruitment rates in the pilot trial will help determine the timescale of recruitment and whether international collaboration should be sought in the definitive study.

If the study proceeds to a definitive trial, statistical comparisons of the primary outcome measure, relapse rate (univariate chi square test or Fisher's exact test, logistic regression multivariable analysis exploring the impact of potential residual confounding will be carried out as a secondary analysis), and of the secondary outcome measures will be made using

appropriate methods (survival analysis for time to relapse, t-test for Achenbach scores, chi square or Fisher's exact test for event data, in all cases appropriate multivariable analysis exploring the impact of potential residual confounding will be carried out as a secondary analysis). Analysis will be of all randomised patients. Missing data will be reported and it is anticipated that there will be no need for statistical interpolation. Any deviations from this plan will be described in the final report.

A Data Monitoring Committee will be established. As this is a pilot trial of two regimes of prednisolone, the drug already used as first line treatment of nephrotic syndrome, it is not anticipated that there will be grounds for early stopping on grounds of efficacy or lack of efficacy. While it is considered that the study is unlikely to be stopped early on safety grounds, all serious unexpected adverse events will be closely considered by the investigators.

## **5. PHARMACOVIGILANCE**

Please refer to Summary of Product Characteristics (appendix A) for known adverse events and expected serious adverse events. On the occurrence of suspected unexpected serious adverse reactions they will be reported to the sponsors not more than 7 working days from when the co-ordinating centre receives the clinician's F7 form according to the Great Ormond Street Hospital NHS Trust GOSH ICH 05/S05/02 Standard Operating Procedure or subsequent updates.

All other Serious Adverse Events/Reactions will be reported to the sponsors within 30 days of receiving the F7 form from the participating site.

All other Adverse Events/Reactions will be recorded on the Follow-up Case Report Forms by the delegated personnel at participating sites and transferred to the F7 form by the co-ordinating centre.

Safety parameters will be assessed, recorded and analysed via Follow-up Case Report Forms and Serious Adverse Event form F7.

The Follow-up forms will be used for eliciting reports of and for recording of inter-current illnesses.

Trial subjects will be followed up for 12 months and following adverse events will be followed up until their participation in the trial ceases. If SUSARs occur, further follow-up may be requested by the chief investigators.

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

The investigators will permit trial-related monitoring, audits, REC review and regulatory inspection(s) providing direct access to source data/documents.

## **7. QUALITY CONTROL AND QUALITY ASSURANCE**

The trial is considered to be low risk, all investigators and staff will follow good clinical practice. 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.

## 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 assent from children and young people under 16. Age appropriate patient information leaflets for children and young people will be provided.

## 9. DATA HANDLING AND RECORD KEEPING

Data to be recorded in the CRFs.

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

Anonymised study records will be sent to trial co-ordinating centre. No personalised data will be kept on study record. Investigators will keep their own study file logs which link patients with anonymised CRFs.

## 10. FINANCING AND INSURANCE

Negligence is covered by NHS arrangements for clinical negligence. The University of Birmingham has clinical trial insurance covering negligent harm for the period 10 February 2005 to 31 August 2007 with a £2,000,000 limit. Non-negligent harm indemnity is provided by the UCL no fault indemnity scheme.

## 11. REFERENCES

1. British Association of Paediatric Nephrology. Consensus statement on management and audit potential for steroid responsive nephrotic syndrome. Report of a workshop by the British Association for Paediatric Nephrology and Research Unit, Royal College of Physicians. *Arch Dis Child* 1994;**70**:151-157
2. Trompeter RS, Lloyd BW, Hicks J, White RH, Cameron JS. Long-term outcome for children with minimal change nephrotic syndrome. *Lancet* 1985;**1**:368-70
3. Brodehl J. Conventional therapy for idiopathic nephrotic syndrome in children. *Clinical nephrology* 1991;**35(S1)**: S8-15
4. ISKDC. Controlled trial of azathioprine in children with nephrotic syndrome. *Lancet* 1970;**1**:959-61
5. Bargman JM. Management of minimal lesion glomerulonephritis: evidence-based recommendations. *Kidney Int Suppl* 1999;**70**:S3-16

6. Ksiazek J, Wyszynska T. Short versus long initial prednisolone treatment in steroid sensitive nephrotic syndrome in children. *Acta Paediatrica* 1995; **84**:889-93
7. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.
8. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software.
9. Evans JHC, Long E. A national audit of nephrotic syndrome: The initial course of prednisolone and outcome. Abstract. *Ped Nephrol* 1998;**12(7)**:C154