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Optimising prednisolone therapy in childhood steroid sensitive nephrotic syndrome: the PREDNOS studies

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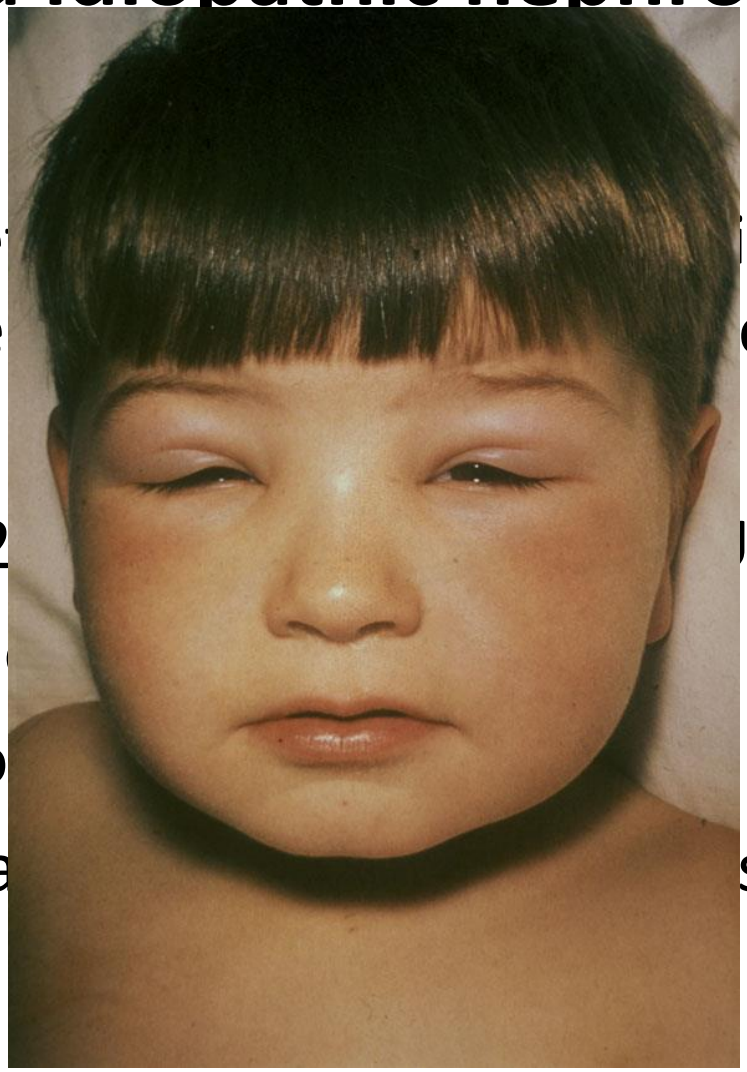
BCTU Investigator meeting 10 05 2018

MANCHESTER 1824
The University of Manchester

UNIVERSITY OF BIRMINGHAM

BCTU
Birmingham Clinical Trials Unit

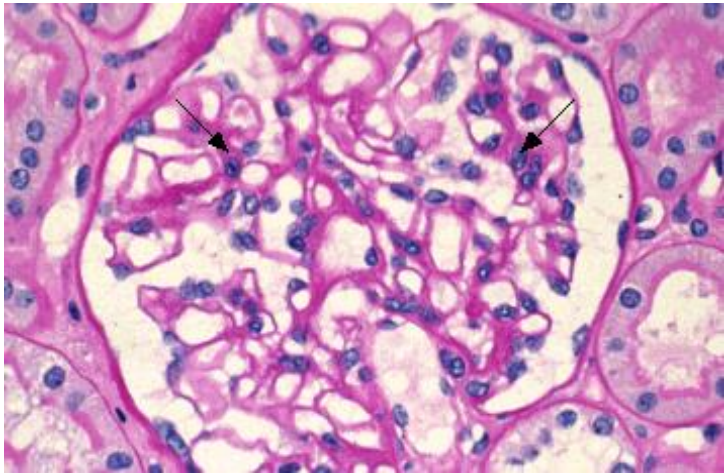
Childhood idiopathic nephrotic syndrome



- Acute onse ith subsequent developme e
- Incidence 2 JK
- Modal age
- Twice as co
- 4-6 x increa sian population

Childhood idiopathic nephrotic syndrome

- Diagnosis based on clinical presentation, low plasma albumin and heavy proteinuria
- Renal function normal
- Highly responsive to corticosteroid therapy
- 80% develop disease relapses
  - Frequently triggered by URTI
- 50% develop frequent disease relapses needing the use of more potent immunosuppressive therapies e.g. cyclophosphamide, ciclosporin, MMF, rituximab



ISKDC regimen

- Prednisone (Prednisolone) 60mg/m^2 (max 80mg) daily for 4 weeks followed by 40mg/m^2 (max 60mg) on alternate days for 4 weeks

- Has been the ‘gold standard’ regimen against which all others have been compared

THE COCHRANE COLLABORATION®

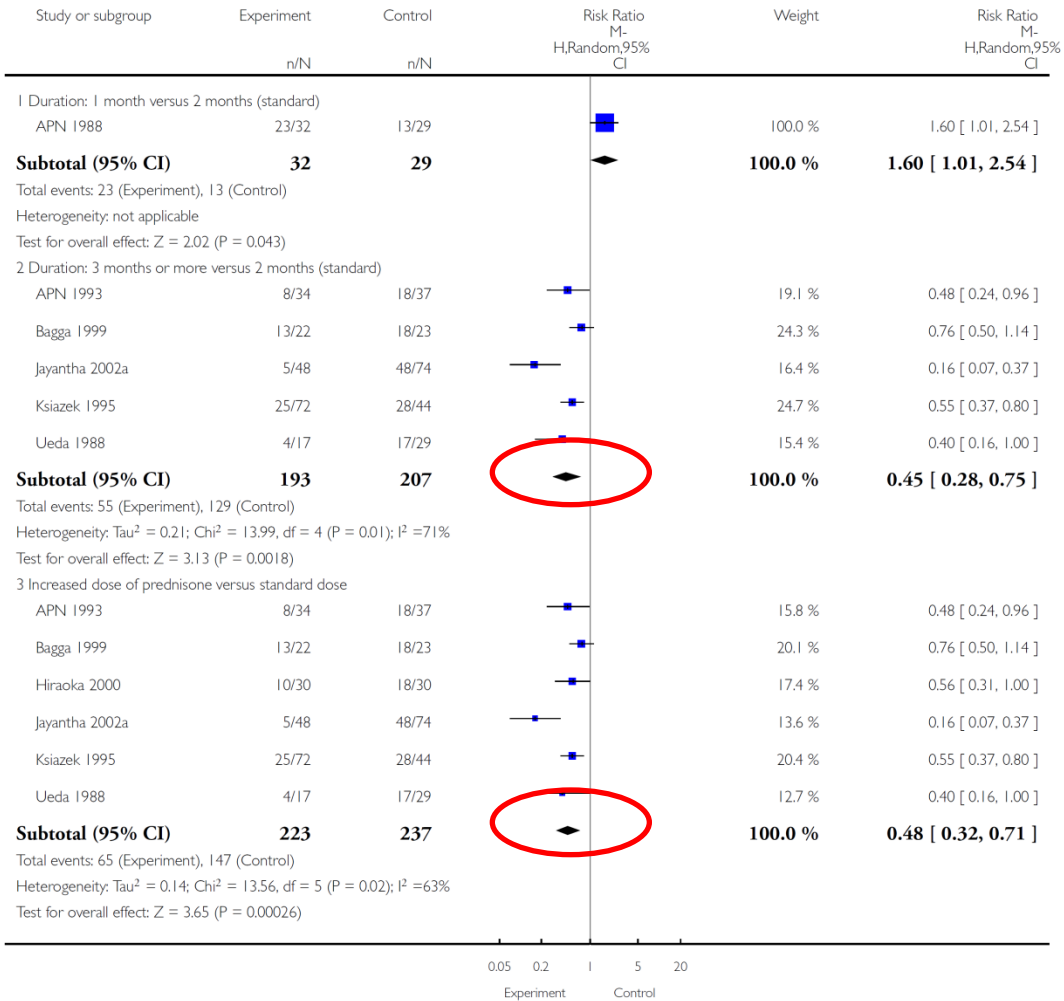
Treatment of the presenting episode of SSNS

Analysis 1.1. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy, Outcome 1 Number of children relapsing by 6 months.

Review: Corticosteroid therapy for nephrotic syndrome in children

Comparison: 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy

Outcome: 1 Number of children relapsing by 6 months



Problems with Cochrane meta-analysis

col is still uncertain. In our study the children were randomly assigned to one of 3 groups, each treated according to a different protocol. The parents had a certain influence on assignment, favouring protocol C. However, the number of children entered was not large and could not have significantly biased the results.

- Cochrane report and further personal discussion confirms requirement for properly conducted, large, double blind, placebo controlled RCT

1º study objective: To determine whether an extended course of prednisolone increases the time to first relapse

2º study objectives: To determine whether extended therapy

i] reduces relapse rate

ii] reduces frequently relapses or steroid dependency

iii] reduces the requirement for 2nd/3rd line therapies

iv] is associated with an increased incidence of steroid-related adverse events including behavioural problems

v] is more cost effective than standard therapy

Power calculation: 116 per arm required to show 20% reduction in relapse rate with 80% power and 2p=0.05

Participants

- Children age 1-14y presenting with first episode of SSNS
- All commenced on open label prednisolone 60mg/m^2 for 4w
- Once steroid sensitivity established, randomised 1:1 to standard or extended course therapy
  - Randomisation minimised to ensure equal distribution of ethnicity (White, S Asian, Other) and age ≤5y, ≥6y)

Protocol

- Regular scheduled study visits to 24m (max 48m)
  - Documentation of relapses, treatment, AEs, interactions with healthcare professionals
  - Comprehensive clinical assessment
  - Questionnaire assessments of behaviour and quality of life
    - Achenbach Child Behaviour Checklist
    - (CHU)-9D
    - PedsQL
- Cost-effectiveness analysis
- Single DNA sample: GWAS study and others

2005

- Pre-MCRN
- Paediatric clinical trial activity in District Hospitals variable but generally sparse
  - Particularly for CTIMPs
- Involvement of District Hospitals essential for successful completion of study
- Need to convince major funders that the trial was feasible

Pilot study

- Funded c.£100k

- Endorsed

Pilot study: Aims

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Pilot study

- Successful in building a collaborative trial network
  - 26 sites fully set up to commence recruitment
  - First patient recruited August 2006
- Total of 55 participants recruited in total of 18 sites
  - 33 boys; mean age 5.5y
  - 39 white, 12 S Asian, 2 mixed race, 2 other
- Recruitment significantly enhanced by the evolution of the NIHR Medicines for Children Research Network

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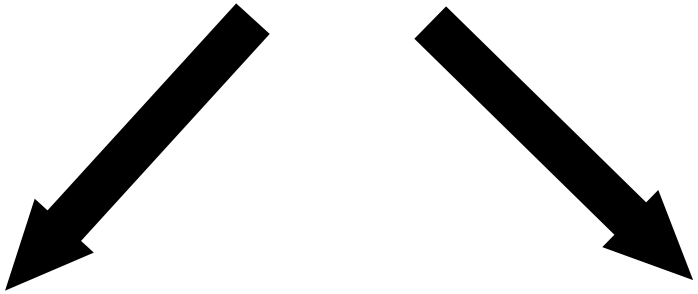
PREDNOS

NHS National Institute for Health Research

MANCHESTER BIOMEDICAL RESEARCH CENTRE

£0.9m funding

225 children with newly presenting SSNS



ISKDC regimen

Total 8 weeks steroids

Then placebo to 16 weeks

Prednisolone 60mg/m^2/d 4w
Then alternate days 60mg/m^2 2w
50mg/m^2 2w
40mg/m^2 2w
30mg/m^2 2w
20mg/m^2 2w
10mg/m^2 2w
Total 16 weeks steroids

First participant randomised 2nd August 2011

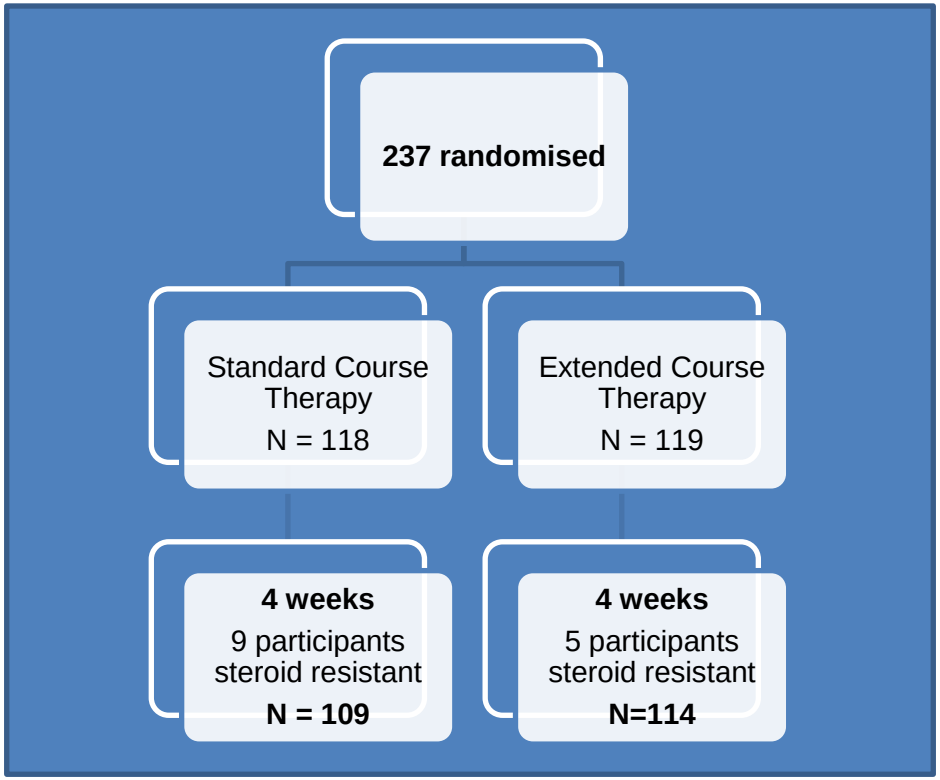
Dr Shankar and team, City General Hospital, Stoke on Trent

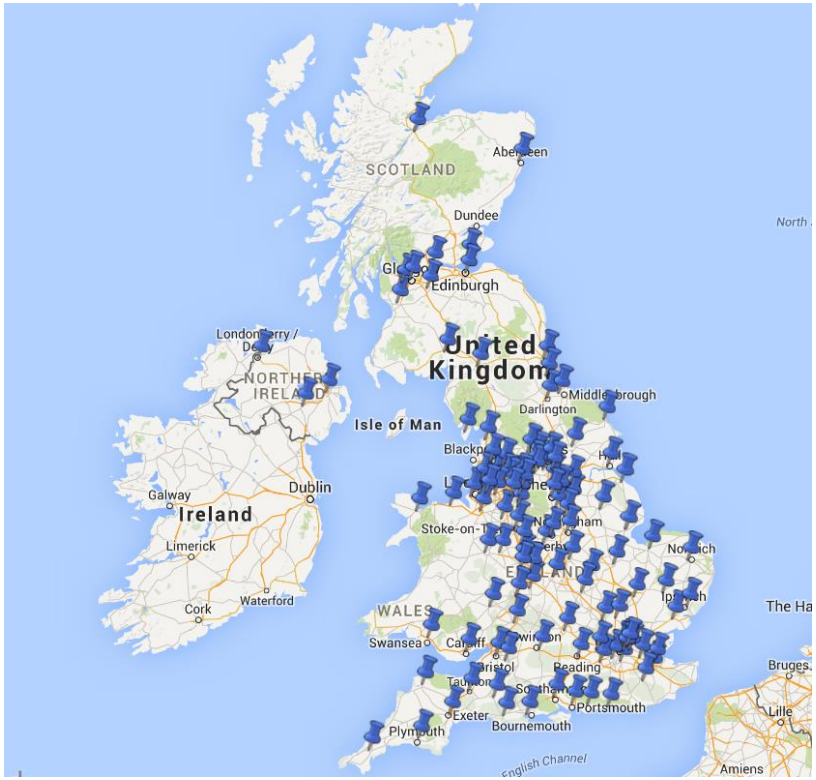
237 participants recruited by 7th October 2014

Total recruitment time 38 months

Results: participants

- 237 randomised in 86 centres





ITT population 213

Results: participants

	Standard course	Extended course	Total
(Total Randomised)	(N=118)	(N=119)	(N=237)
Steroid Sensitive Patients (ITT cohort)	**N=109**	**N=114**	**N=223**
Age (mean [SD]) (in years)	4.7 (2.9)	5.1 (3.2)	4.9 (3.1)
Age ≤5 years	72 (66)	73 (64)	145 (65)
Sex male	78 (72)	68 (60)	146 (65)
Ethnicity: South Asian	21 (19)	23 (20)	44 (20)
White	73 (67)	75 (66)	148 (66)
Other / Not Stated	15 (14)	16 (14)	31 (14)
Open label prednisolone dose (mean [SD]) $mg/m^2/day$	58.5 (5.9)	58.0 (6.8)	58.2 (6.4)

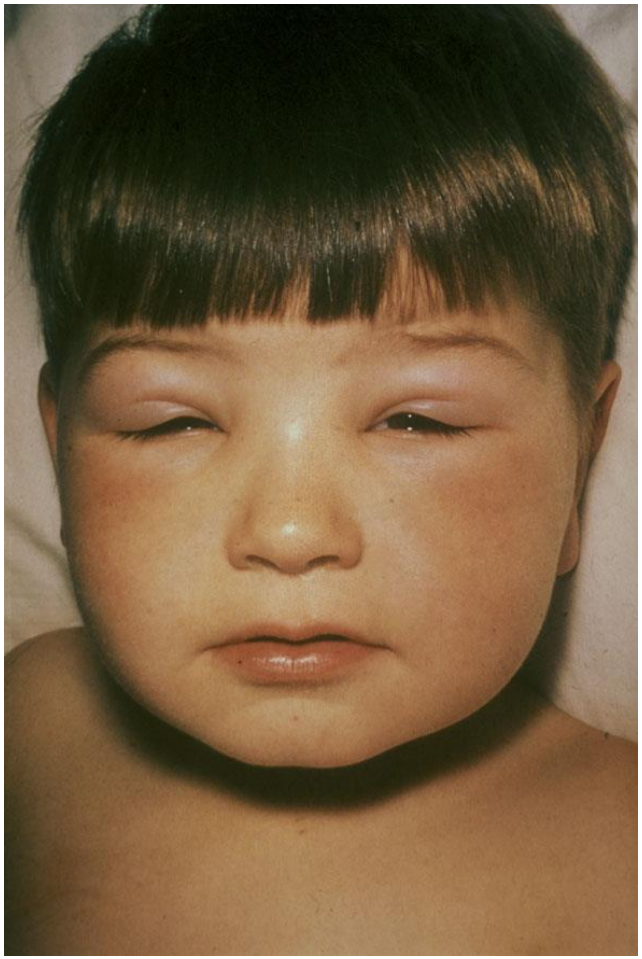
Recruitment in tertiary nephrology centres

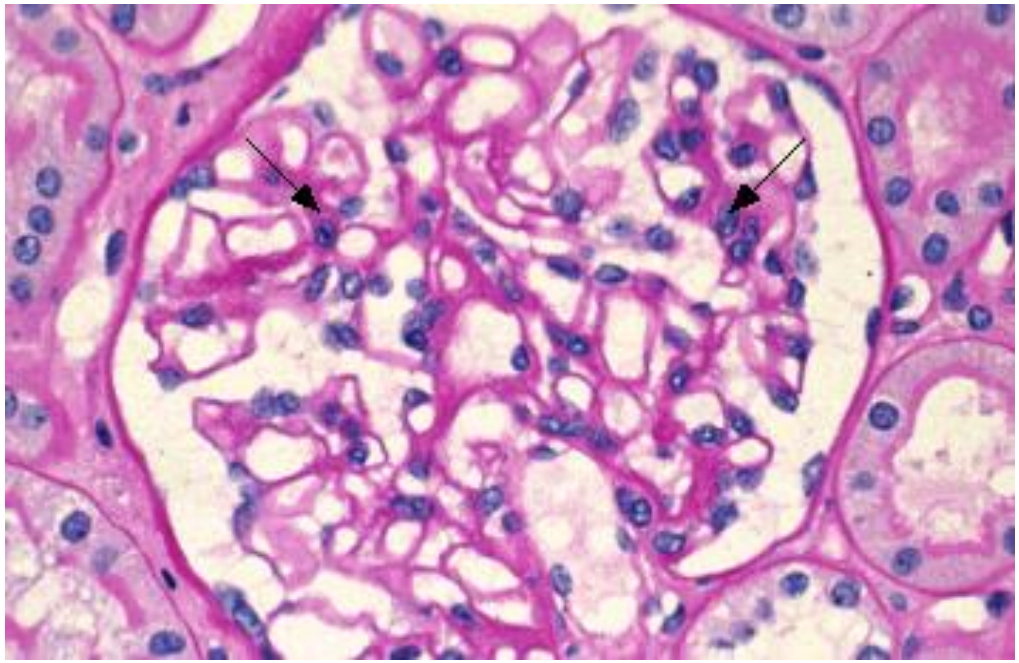
Centre	Randomised
Manchester	18
Liverpool	10
Nottingham	9
Bristol	8
Glasgow	7
Cardiff	6
Birmingham	5
Newcastle	5
Belfast	4
Evelina	3
Leeds	3
GOS	1
Southampton	1

Recruitment in district centres

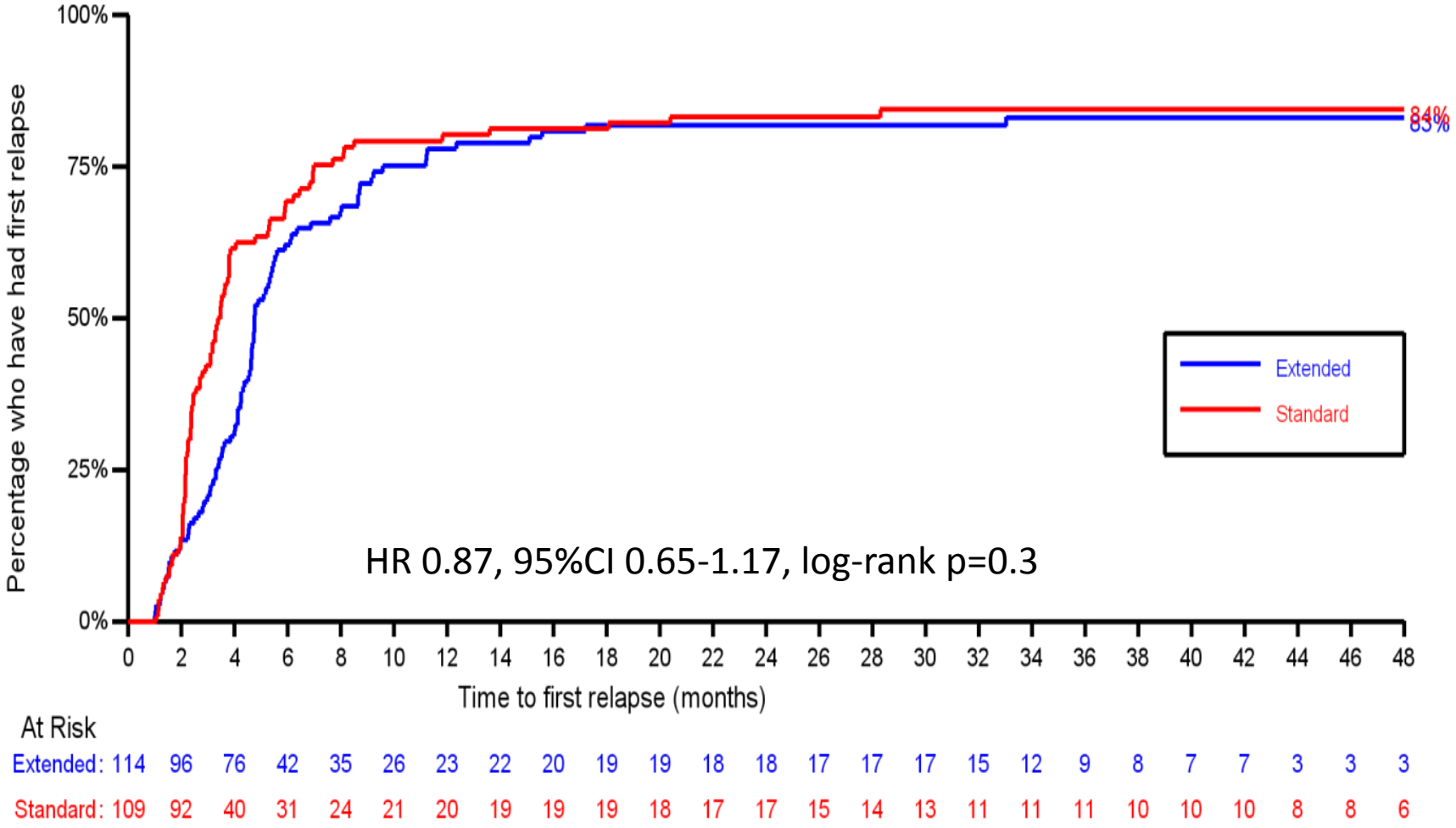
Centre	Randomised
Leicester	16
Gloucester	6
Blackburn	5
Bradford	5
Ashford	4
Bolton	4
Kettering	4
Oxford	4
Chester, Derby, Rhyl, Lincoln, Maidstone, Newham, Norwich, Royal Berks, Portsmouth, Tameside	3

Results





Primary end point: No difference in time to first relapse



Results: secondary end-points

End-point	SC (N=109)	EC (N=114)	p value
Total number of relapses	3.61	3.98	0.4
FRNS	50%	53%	0.7
SDNS	44%	42%	0.8
Requiring 2nd or 3rd line immunosuppressive therapy	56%	54%	0.8
Total prednisolone dose received	5475mg	6674mg	0.07

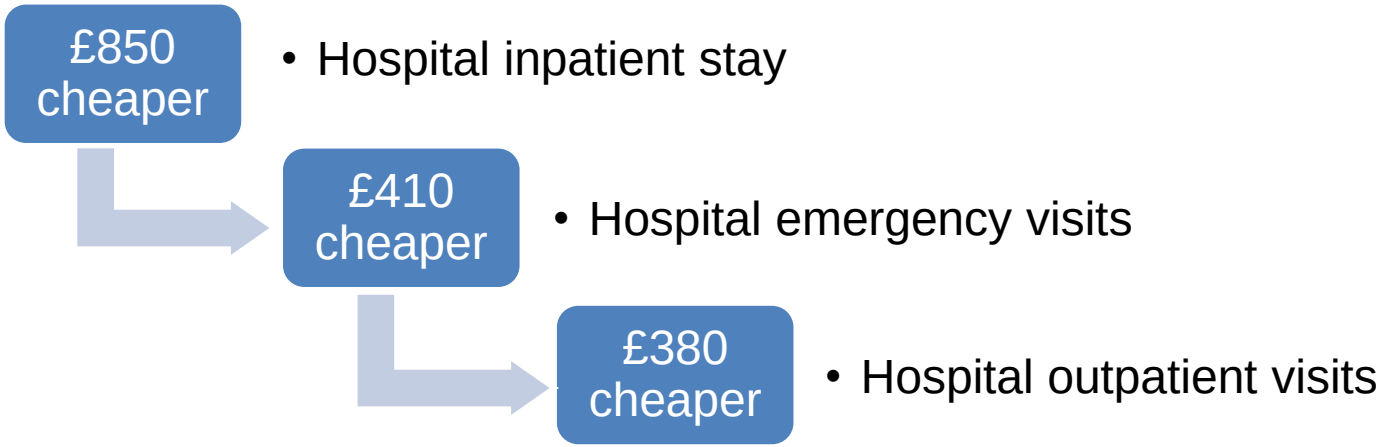
Adverse effects

Adverse Event	SC group (N=109)	EC group (N=114)	RR (95% CI)
Cushingoid facies	78 (71%)	83 (73%)	1.02 (0.88-1.19)
Striae	7 (6%)	14 (12%)	1.92 (0.81-4.54)
Hypertrichosis	41 (38%)	45 (39%)	1.05 (0.77-1.45)
Acne	7 (6%)	12 (11%)	1.64 (0.68-3.99)
Increased appetite	103 (94%)	106 (93%)	1.00 (0.94-1.07)
Poor behaviour	101 (93%)	94 (82%)	0.90 (0.82-0.98)
Glycosuria	14 (13%)	19 (17%)	1.34 (0.72-2.48)
Cataract	1 (1%)	1 (1%)	0.96 (0.06-15.00)
Abdominal pain	51 (47%)	49 (43%)	0.91 (0.69-1.20)

- No difference in Achenbach CBC scores

Health economics

Per patient	Standard course	Extended course	95% Confidence interval
Mean QALYs	1.7908	1.8070	0.0162 (-0.0047 to 0.0372)
Mean cost	£ 4,369	£ 2,696	- £1,672 (- £3,455 to £109)



- 1 QALY (Full health for one year) = £20,000
  - Therefore 0.0162 QALY gained from EC is equivalent to £324
- Overall, the probability of saving cost with EC is 98%

Conclusions 1

- The PREDNOS study has shown no evidence of clinical benefit of extending initial prednisolone therapy in SSNS beyond the 8 week regimen described by the ISKDC

- However, the EC regimen was associated with an increase in generic health benefit and significant cost savings

Recent studies

http://www.kidney-interr

see commentary

Extendin
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Mani Kalaivani[6], F

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see clinical trial on pages 217 and 225

New lessons from randomized trials in steroid-sensitive nephrotic syndrome: clear evidence against long steroid therapy

Peter F. Hoyer[1]

The best initial therapy for steroid-sensitive nephrotic syndrome (SSNS) in children is subject to ongoing debate. Systematic reviews and meta-analyses have concluded that at least 3 months and up to 7 months of treatment would reduce the number of relapses by 30%. But summarizing small underpowered studies cannot eliminate the basic flaws in design. Two well-powered randomized prospective trials now come to the opposite conclusion, and these results should impact the management of children with SSNS.

Kidney International (2015) **87,** 17–19. doi:10.1038/ki.2014.354

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ollege, Aligarh, India;
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Corticosteroid therapy for nephrotic syndrome in children: 2015 update

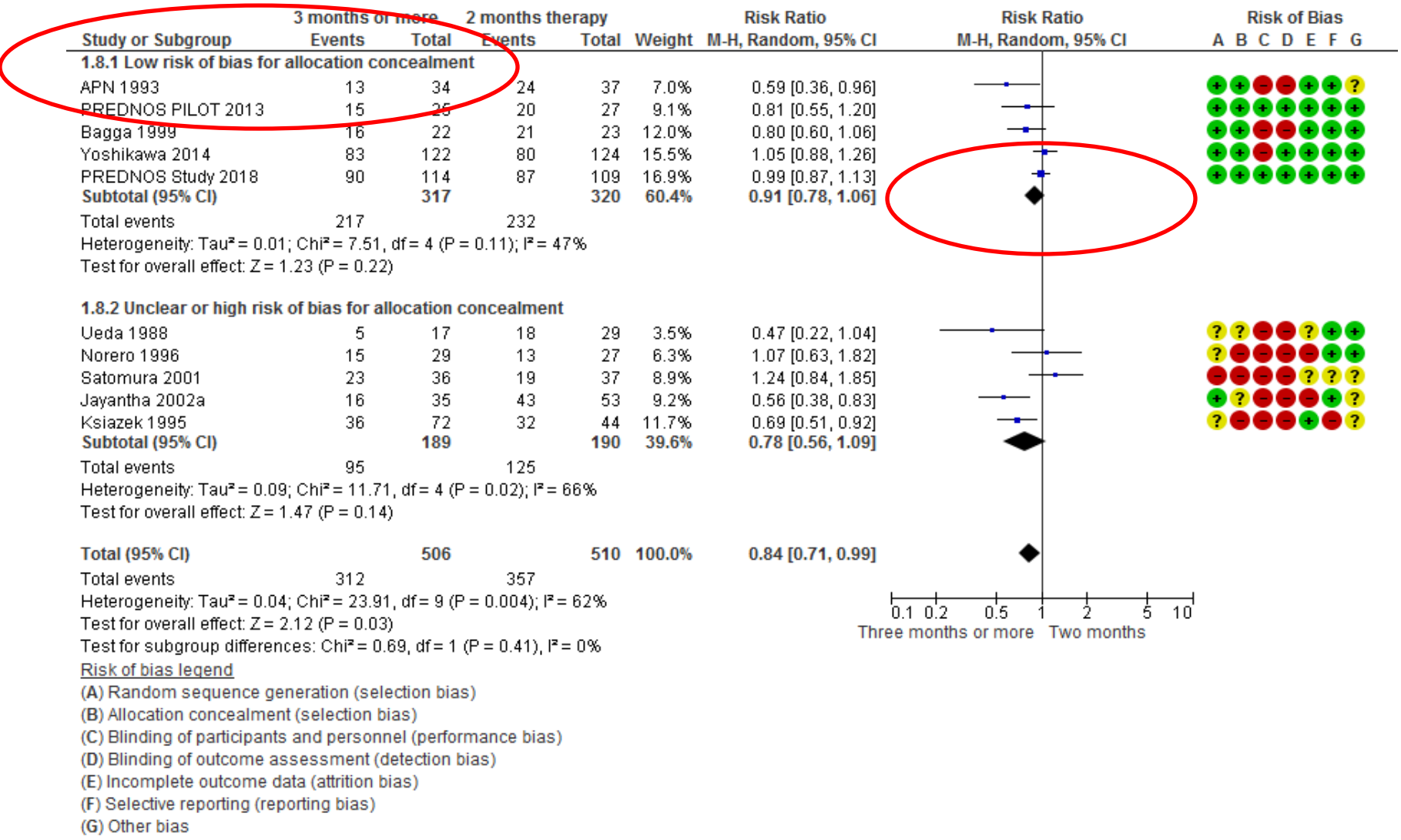
Implications for practice

Prolongation of prednisolone therapy beyond two to three months in the initial episode of SSNS does not reduce the risk of relapse in studies at low risk of bias whether the same total dose of prednisone is used for short and long durations or whether the total dose of prednisone is increased with longer durations of treatment.

The results of a further well designed study evaluating different durations and therefore total doses of prednisone are awaited (PREDNOS Study 2013).

Cochrane meta-analysis

Number of participants who developed a relapse by 12-24m

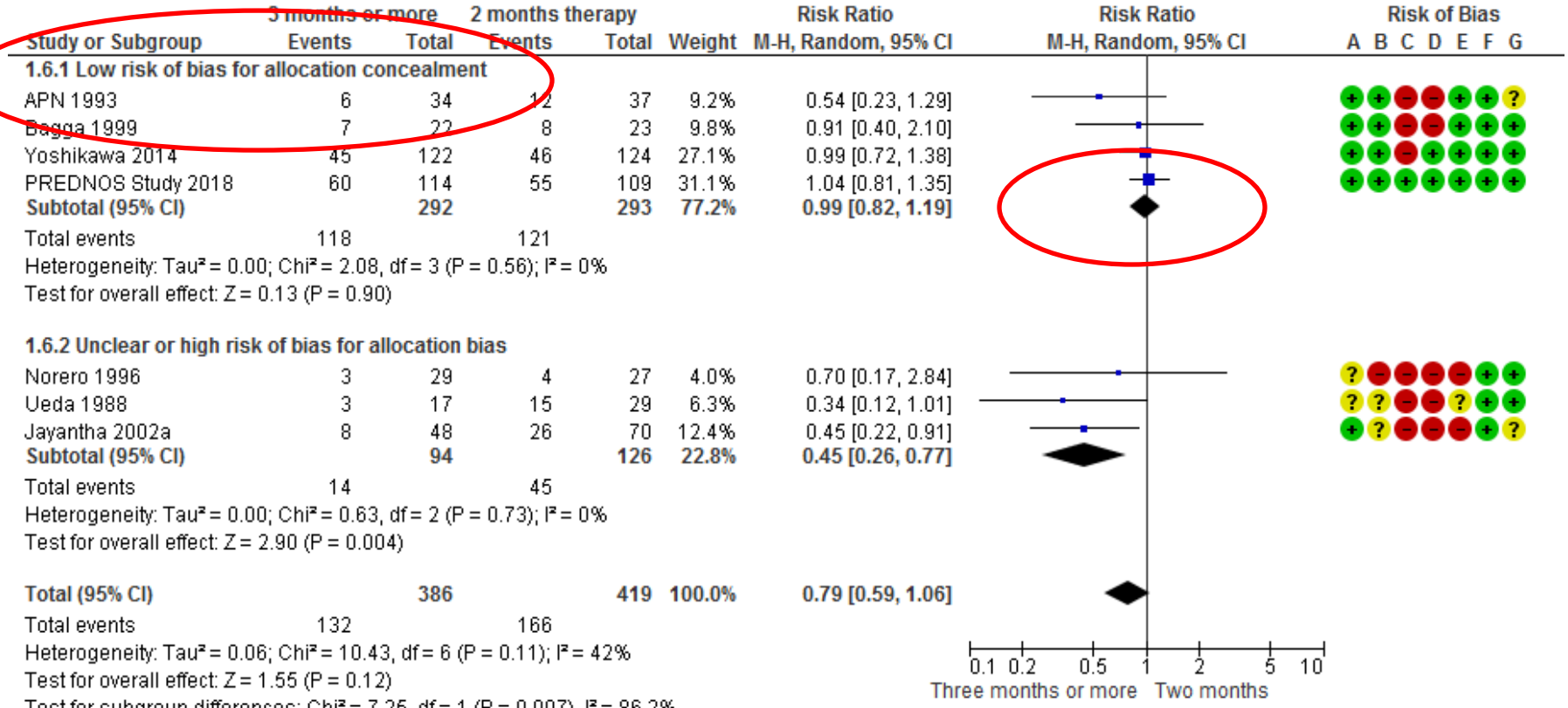


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Cochrane meta-analysis

Number of participants developing frequently relapsing SSNS by 12-24m



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(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

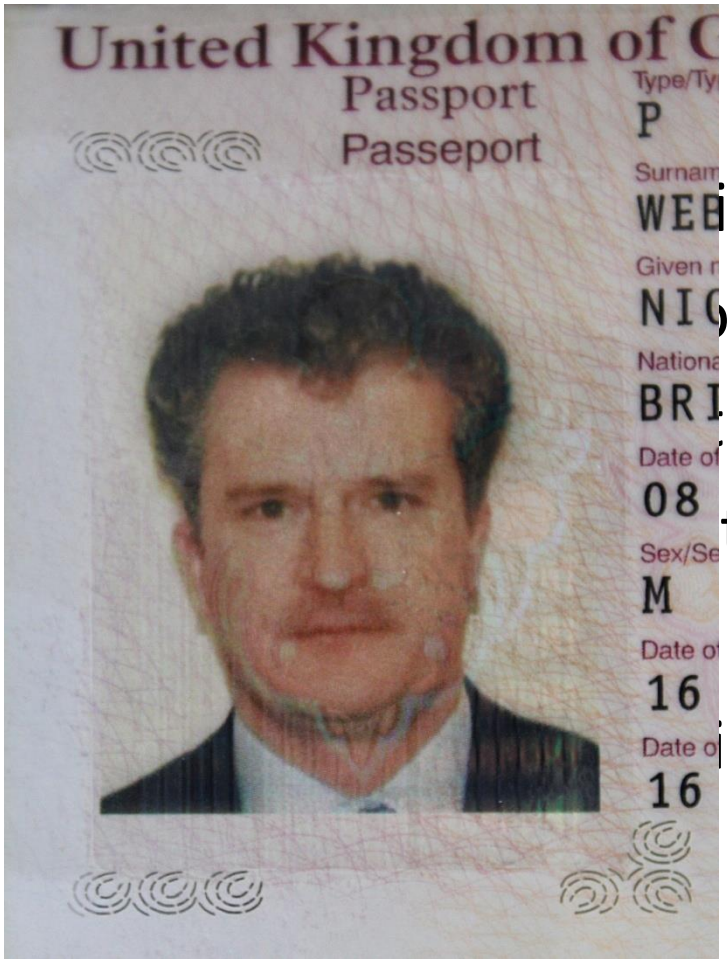
Conclusions 2

- Cochrane systematic review 2017 shows no benefit in the prolongation of corticosteroids beyond the 2 month regimen first proposed by the ISKDC

PREDNOS study: Outputs

- Oral presentation at ESPN
- Manuscript published in **Pharmacoeconomics** (IF 3.3)
  - Mapping the Paediatric Quality of Life Inventory (PedsQL™) Generic Core Scales onto the Child Health Utility Index–9 Dimension (CHU-9D) Score for Economic Evaluation in Children
- Main data about to be submitted to BMJ
  - Combined publication of clinical and health economic data

PREDNOS study timelines



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Evolution of PREDNOS 2 - URTI and relapses

- Around 50% of relapses are preceded by an URTI
- If URTI develops, around 50% chance of a relapse developing
- It seems logical that URTI is pivotal and attempts to ameliorate the URTI driven process are appropriate

Pre-emptive treatment of relapses

Gulati *et al*. Clin J Am Soc Nephrol 2011; 6: 63-69

- 100 children - FRNS on AD prednisolone (32 on levamisole)
- At time of development of URTI randomised to 7 days of
  - **daily prednisolone** at same dose
  - **Remained on AD prednisolone**
- URTI defined as
  - Fever >38, rhinorrhoea, cough, diarrhoea
- Incidence of URTI-related relapse reduced
  - Relapse rate reduced by 0.7/y (95%CI 0.3-1.1: $p<0.01$)

Unanswered questions

- Utility of this approach in Western children
  - Different pattern of URTI – less fever, diarrhoea etc.
- Utility in children receiving other therapies
  - ciclosporin, tacrolimus, MMF, cyclophosphamide, rituximab +/- AD prednisolone?
- Cost-effectiveness
- Adverse-effect risk?
  - Particularly effect on behaviour

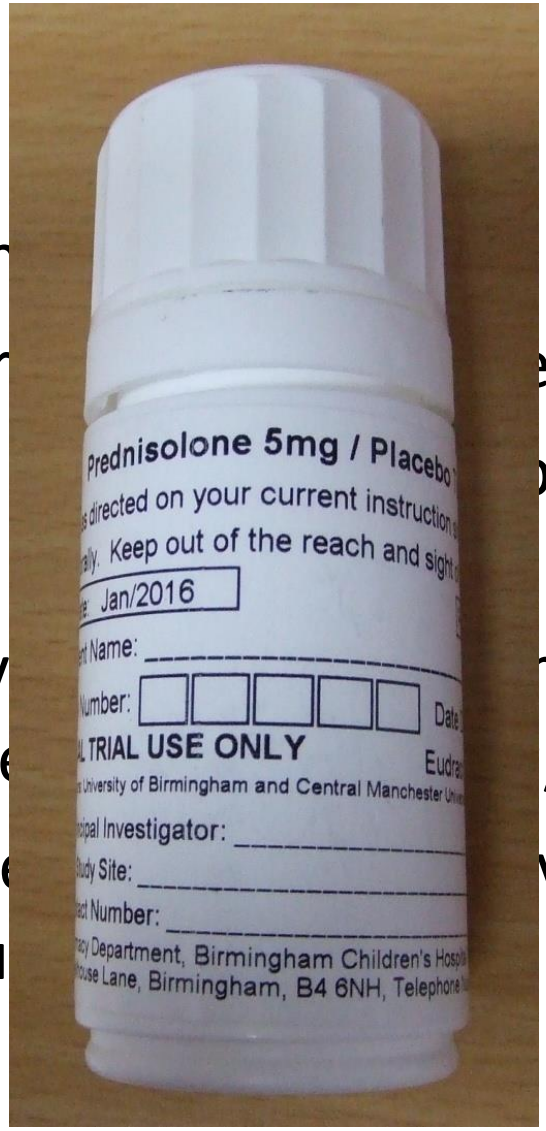
PREDNOS 2: Primary study objective

- To determine whether a six day course of oral prednisolone given at the time of URTI reduces the incidence of first URTI-related relapse

NIHR Health Technology Assessment programme funded project

PREDNOS 2

- 360 UK children lapses in past 12m)
- On any long-ter essive regimen
- Randomised to placebo arm at study entry
- When URTI dev mmence child on 6 days of daily pre /m2) or placebo
- Repeated with e velops over 12 month follow-u



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PREDNOS 2

- URTI defined as the presence of at least 2 of the following *for at least 24 hours*:
  - sore throat
  - ear pain/discharge
  - runny nose
  - cough (dry/barking)
  - hoarse voice
  - fever >37^{O}C (measured using tympanometric electronic thermometer)

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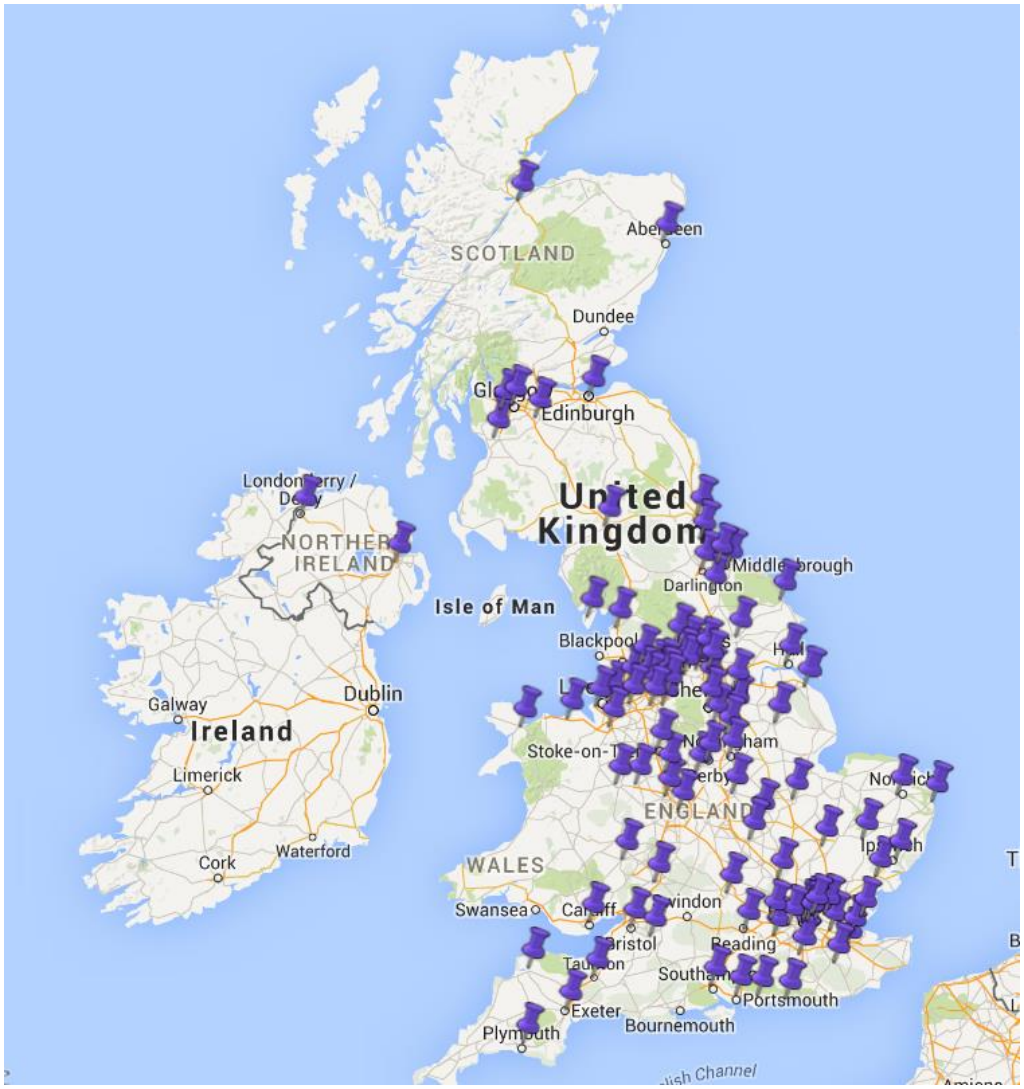
PREDNOS 2

- Primary end-point – development of URTI-related relapse
- Secondary end points – relapse rate, cumulative prednisolone dose, adverse events (particularly behavioural), escalation / de-escalation of background immunosuppressive therapy
- Quality of Life Assessment
- Formal Health Economic Analysis (Frew, Birmingham)
- DNA sampling

Recruitment



- First participant recruited 19.3.13
- Total 326 participants recruited
- 116 sites set-up
- 64 have recruited participants
- Further sites currently in set-up

Corticosteroid therapy for nephrotic syndrome in children: 2017 update

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Conclusions

- The PREDNOS studies have illustrated
  - Large scale multicentre paediatric studies in District Hospitals are entirely deliverable in the UK
    - Great willingness of DGH paediatricians to participate
- PREDNOS studies are answering clinically important questions
  - Results likely to influence future UK (and international) practice
  - Translation into changes in patient care could take place over a very short time period

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Acknowledgments

- Participants and their families
- Paediatric Nephrologists and General Paediatricians across UK
- NIHR HTA, Kidney Research UK and Kids Kidney Research for funding support
- NIHR MCRN and CRN
- Birmingham CTU
- Birmingham Children's Hospital Pharmacy

Thank you

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