Supplementary Material
With the manuscript entitled:

*Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome*

Running title: RCT childhood nephrotic syndrome

By:

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**Supplementary Table 1.** Currently reported prednisolone regimens for the first episode of childhood nephrotic syndrome.

| Initial prednisolone regimen | Duration | Cumulative dose | Reported use |
|---|---|---|---|
| *ISKDC:*<br>4 weeks 60 mg/m$^2$ daily<br>4 weeks 40 mg/m$^2$ on 3 out of 7 days or on alternate days | 8 weeks | 2240 mg/m$^2$ | Canada,[1] Nigeria,[2] South-Korea,[3] UK,[4] USA[5] |
| *BAPN:*<br>60 mg/m$^2$ daily until remission<br>4 weeks 40 mg/m$^2$ on 3 out of 7 days or on alternate days | Maximum 8 weeks | Maximum 2240 mg/m$^2$ | UK[6] |
| *APN :*<br>6 weeks 60 mg/m$^2$ daily<br>6 weeks 40 mg/m$^2$ on alternate days | 12 weeks | 3360 mg/m$^2$ | Canada,[1] Germany,[7] Japan,[8] The Netherlands,[9] Spain,[10] USA[5] |
| *SNP:*<br>4 weeks 60 mg/m$^2$ daily<br>8 weeks 60 mg/m$^2$ on alternate days<br>2 weeks 45 mg/m$^2$ on alternate days<br>2 weeks 30 mg/m$^2$ on alternate days<br>2 weeks 15 mg/m$^2$ on alternate days | 18 weeks | 3990 mg/ m$^2$ | France[11] |
| Modifications of one or more of the regimens described above | 4-24 weeks | uncertain | Australia,[12] Brazil,[13] Egypt,[14] India,[15] Poland,[16] Taiwan,[17] Turkey,[18] USA[5] |

ISKDC, International Society of Kidney Disease in Children; APN, Arbeitsgemeinschaft für Pädiatrische Nephrologie; BAPN, British Association for Pediatric Nephrology; SNP, Société de Néphrologie Pédiatrique.

**Supplementary Table 2.** Comparison of baseline characteristics between randomized and not randomized patients.

| Variable | Randomized, started trial medication (n=126) | Randomized, did not start trial medication - withdrawn consent (n=13) | Randomized, did not start trial medication – SRNS (n=11) | Not Randomized (n=57) | p |
|---|---|---|---|---|---|
| Male, n (%) | 86 (68) | 11 (85) | 5 (45) | 35 (62) | 0.193 |
| Age at diagnosis; median (IQR) | 4.2 (3.2-6.2) | 3.0 (2.5-4.7) | 4.1 (3.1-9.3) | 4.6 (2.7-8.4) | 0.218 |
| Hospital, University (%) | 14 (11) | 4 (31) | 2 (18) | 5 (9) | 0.136 |

**Supplementary Table 3a.** Nine patients fulfilling clinical yet not strict FRNS

| Study ID | Treatment group | Indication | Diagnosis | End of randomized treatment | Relapses and additional treatment (indicated with →) | Crit A | Crit B | Crit C | SD |
|---|---|---|---|---|---|---|---|---|---|
| 28 | 6 months | very early onset SDNS + secondary SRNS | 2 -11-2005 | 19-04-2006 | 28-2-2006[a]<br>31-3-2006[a]<br>No remission after 6 wks pred: secondary SRNS → ciclosporin<br>26-1-2009 | No | No | Yes | Yes |
| 52 | 6 months | 3 relapses within a time frame of 9 months | 07-04-06 | 22-09-06 | 5-6-2007<br>22-11-2007<br>26-3-2008<br>16-8 -2008 → cyclophosphamide | No | No | Yes | No |
| 90 | 3 months | secondary SRNS | 11-1 -2007 | 05-04-2007 | 18-3-2007[a]<br>No remission after 6 wks of pred: secondary SRNS → mycophenolate mofetil<br>15-5-2008 → ciclosporin | No | No | Yes | No |
| 119 | 3 months | 3 relapses within a time frame of 8 months + behavioural problems + high BP | 17-9 -2007 | 10-12-2007 | 3-5-2008<br>17-11-2008<br>6-1-2009 → cyclophosphamide<br>7 -7 -2009<br>13-4 -2010 → levamisole | No | No | Yes | No |
| 129 | 3 months | very early onset SDNS + secondary SRNS | 31-12-2007 | 24-03-2008 | 28-2-2008[a]<br>17-3-2008[a]<br>No remission after 6 wks of pred: secondary SRNS → ciclosporin<br>16-8-2011 | No | No | Yes | Yes |
| 135 | 6 months | very early onset SDNS | 28-2 -2008 | 14-08-2008 | 13-6-2008[a]<br>29-7-2008[a]<br>21-10-2008[a] →cyclophosphamide<br>9 -2 -2011 | No | No | Yes | Yes |
| 142 | 6 months | very early onset SDNS + partial secondary steroid resistance | 5 -4 -2008 | 20-09-2008 | 30-6-2008[a]<br>Partial remission after 6 wks oral prednisolone → IV prednisolone: remission<br>15-10-2008[a] → IV prednisolone + ciclosporin<br>17-8-2009<br>6 -11-2009[a]<br>22-12-2009[a] → mycophenolate mofetil<br>5 -4 -2011[a] | No | No | Yes | Yes |
| 150 | 6 months | 2 relapses within a time frame of 3 months + behavioural problems at high doses | 8 -8 -2008 | 23-01-2009 | 22-1-2009[a]<br>12-4-2009 → prednisolone maintanance | No | No | Yes | No |
| 153 | 6 months | 2 relapses within a time frame of 3 months | 21-8 -2008 | 05-02-2009 | 14-1-2009[a]<br>30-3-2009 → prednisolone maintanance | No | No | Yes | No |

[a]During or within two weeks after cessation of prednisolone. Very early onset SDNS, the first two relapses occurred during or within 2 weeks after cessation of prednisolone; FRNS, frequently relapsing nephrotic syndrome; SDNS, steroid dependent nephrotic syndrome. BP, blood pressure.

**Supplementary Table 3b.** Occurrence of a first relapse and clinical FRNS according to each criterion.

| Time (months) | Relapse | NAR (relapse) | Clinical FRNS | NAR (Clinical FRNS) | A | B | C |
|---|---|---|---|---|---|---|---|
| 3 month-group | | | | | | | |
| 0 | 0 | 62 | 0 | 62 | | | |
| 3 | 1 | 61 | 2 | 60 | | | 2 |
| 6 | 29 | 32 | 9 | 51 | 9 | | |
| 9 | 6 | 26 | 14 | 37 | 14 | | |
| 12 | 6 | 20 | 1 | 36 | | 1 | |
| 15 | 3 | 17 | 1 | 35 | | 1 | |
| 18 | 0 | 17 | 2 | 33 | | 1 | 1 |
| 21 | 1 | 15 | 2 | 30 | | 2 | |
| 24 | 2 | 12 | 0 | 26 | | | |
| >24 | 0 | <12 | 0 | <26 | | | |
| **Total** | **48** | | **31** | | **23** | **5** | **3** |
| 6 month-group | | | | | | | |
| 0 | 0 | 64 | 0 | 64 | | | |
| 3 | 5 | 59 | 0 | 64 | | | |
| 6 | 18 | 41 | 5 | 59 | | 2 | 3 |
| 9 | 11 | 30 | 15 | 44 | 12 | 3 | |
| 12 | 7 | 23 | 10 | 34 | 6 | 2 | 2 |
| 15 | 3 | 20 | 1 | 32 | | 1 | |
| 18 | 4 | 16 | 1 | 31 | | 1 | |
| 21 | 2 | 14 | 2 | 29 | | 2 | |
| 24 | 0 | 13 | 0 | 26 | | | |
| >24 | 1 | <13 | 4 | <26 | | 3 | 1 |
| **Total** | **51** | | **38** | | **18** | **14** | **6** |

Data other than NAR represent numbers of patients with an event within time periods of 3 months. A: ≥ 2 relapses within six months after completing initial treatment; B: ≥ 4 relapses within any period of 12 months, including relapses during initial treatment; C: clinical decision that included additional intervention: prednisolone maintenance therapy (> three months) or other immunosuprressive agents. NAR, number at risk; FRNS, frequently relapsing nephrotic syndrome.

**Supplementary Table 4.** Characteristics of studies comparing 3 to 6 months prednisolone for the first episode of childhood nephrotic syndrome.

| Study | Publication Status | Design and Setting | Inclusion Criteria | Definition of FRNS | Short Regimen | Long Regimen | Relapse Treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|
| Ksiazek 1995[19] | Fully published | Single centre, renal centre, Poland<br>Inadequate concealment of allocation<br>No blinding: parents chose regimen<br>Loss of follow up: 0%<br>Intention to treat analysis | First episode of NS<br>Age 13 months – 11 years<br>Remission within 4 weeks of daily prednisolone | ≥ 2 relapses within 6 months after remission or<br>4 relapses within any 12 months * | 3 months<br><br>2530 mg/m$^2$ (e)<br>n=68 | 6 months<br><br>3070 mg/m$^2$ (e)<br>n=72 | Within 6 months after completing initial regime: 1 mg/kg daily until remission + 1 mg/kg on alternate days for 4 weeks<br><br>> 6 months after completing initial regime: according to the long regimen | 27 months and 30 months respectively |
| Gulati 2001[20] | Abstract only | Single centre, renal centre, India*<br>Adequate concealment of allocation<br>No blinding<br>Loss of follow up: 4%<br>No intention to treat analysis | First episode of NS | >2 relapses within any 6 months or<br>> 6 relapses within any 18 months* | 3 months<br><br>3360 mg/m$^2$<br>n=70 | 6 months<br><br>4200 mg/m$^2$<br>n=70 | Not stated | 15 months and 18 months respectively* |
| Hiraoka 2003[8] | Fully published | Multicentre, renal centres, Japan<br>Adequate concealment of allocation<br>No blinding<br>Loss of follow up: 3%<br>Modified intention to treat analysis | First episode of NS | ≥ 2 relapses within any 6 months after completing the previous regimen | 3 months<br><br>3360 mg/m$^2$<br>n=34 | 6 months<br><br>4620 mg/m$^2$<br>n=36 | 6o mg/m$^2$ daily until remission + 40 mg/m$^2$ on alternate days for 4 weeks | Median 34 months (range 15-48) |
| Pecoraro 2004[21] | Abstract only | Single centre, renal centre, Italy*<br>Inadequate concealment of allocation<br>No blinding<br>Loss of follow up: not stated<br>No intention to treat analysis | First episode of NS | Not stated | 3 months<br><br>3094 mg/m$^2$ (e)<br>n=16 | 6 months<br><br>5235 mg/m$^2$ (e)<br>n=16 | Not stated | No median or minimum stated; maximum 21 months |
| Mishra 2012[22] | Fully published | Single centre, renal centre, India<br>Unclear concealment of allocation<br>No blinding<br>Loss of follow up: 3%<br>No intention to treat analysis | First episode of NS<br>Age 1-10 years<br>No underlying disease<br>remission within 4 weeks of daily prednisolone | Not stated | 3 months<br><br>3360 mg/m$^2$<br>n=37 | 5 months<br><br>3990 mg/m$^2$ (e)<br>N=37 | 2 mg/kg daily until remission + 1.5 mg/kg for 4 weeks | 12 months |
| Current Study | Submitted | Multicentre, general and university centres, Netherlands (1 Belgian)<br>Adequate concealment of allocation<br>Double blinding<br>Loss of follow up: 1%<br>Modified intention to treat analysis | First episode of NS<br>Age 9 months - 17 years<br>No underlying disease | ≥ 2 relapses within 6 months after completing initial regime or<br>4 relapses within any 12 months** | 3 months<br><br>3360 mg/m$^2$<br>n=62 | 6 months<br><br>3390 mg/m$^2$<br>n=64 | 6o mg/m$^2$ daily until remission + 40 mg/m$^2$ on alternate days for 4 weeks | Median 47 months (IQR 35-60) |

Search strategy: we searched Medline and abstract books from the International Pediatric Nephrology Association and the European Society for Pediatric Nephrology for studies comparing three months prednisolone therapy to longer prednisolone regimens for the first episode of childhood NS, published since the last updated Cochrane meta-analysis.[23] We searched between Jan 1 2007 and May 31 2012. Search terms included "nephrotic", "syndrome", and "prednisolone" or "prednisone". e, estimated; * not stated in the original article/abstract, yet taken from reference[23]; **stated as strict FRNS.

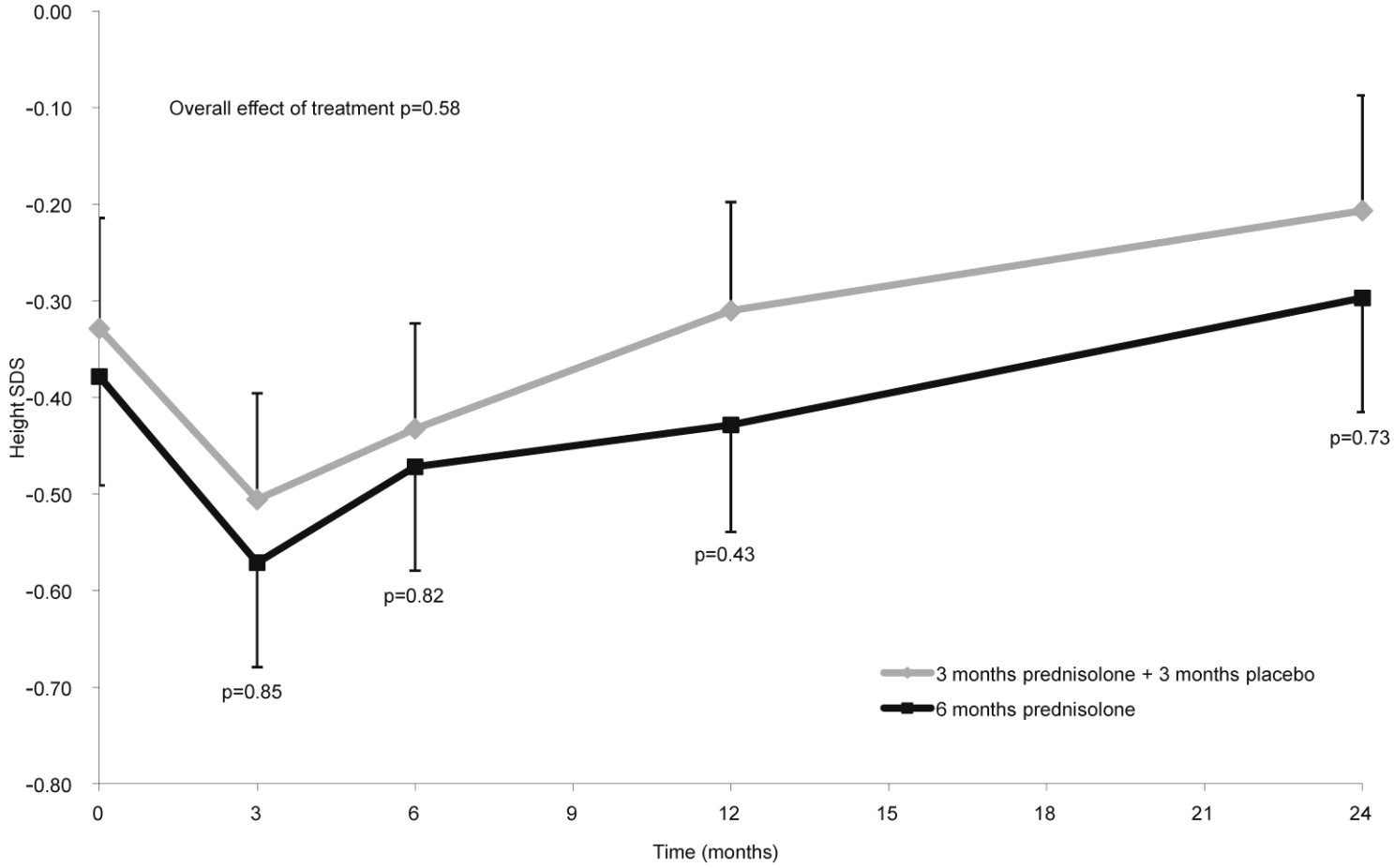
**Supplementary Table 5a.** Numbers of patients reported and enrolled per hospital

| Number of patients per site | Reported, number of hospitals | Enrolled, number of hospitals | Not Enrolled, number of hospitals | Enrollment Ratio | |
|---|---|---|---|---|---|
| | | | | Quartiles | Number of hospitals |
| 1 | 28 | 29 | 31 | 0 - 0.25 | 12 |
| 2 | 20 | 19 | 7 | 0.26 - 0.5 | 11 |
| 3 | 15 | 12 | 3 | 0.51 - 0.75 | 15 |
| 4 | 8 | 8 | 0 | 0.76 - 1.0 | 44 |
| 5 | 7 | 3 | 0 | | |
| 6 | 1 | 0 | 0 | | |
| 7 | 2 | 0 | 0 | | |
| 8 | 0 | 0 | 1 | | |
| 12 | 1 | 0 | 0 | | |
| Total (hospitals) | 82 | 71 | 42 | | |
| Total (patients) | 212 | 150 | 62 | | 82 |
| | Reported per hospital | Enrolled per hospital | Not enrolled per hospital | | |
| Median number of patients (IQR) | 2 (1-3) | 2 (1-3) | 1 (0-1) | Median 0.8 (0.5-1.0) | |

This table shows the numbers of hospitals reporting, enrolling, or not enrolling a certain number of patients. Example: Eight hospitals have each reported 4 patients, 12 hospitals have each enrolled three patients. In total, 93 hospitals (84 general and 9 university hospitals) participated in the study. 82 hospitals reported patients for assessment of eligibility (n=212). 71 hospitals (due to reorganization currently 69 hospitals) enrolled patients (n=150). The majority of these hospitals enrolled one to three patients; The median enrollment ratio was 0.8. IQR, inter quartile range.

**Supplementary Table 5b.** Reasons for not participating (more than one reason is possible)

| Reason | Number of cases |
|---|---|
| Fear of blinding/placebo | 7 |
| Insufficient understanding of the study protocol due to: | |
| - Language | 10 |
| - Intelligence | 3 |
| Fear of research settings in general | 9 |
| Burden considered too high: | |
| - Six months study medication considered too long | 14 |
| - Parental distress at the time of diagnosis | 4 |
| - Child considered too young to participate | 4 |
| - Additional testing/questionnaires | 3 |
| - Child would get too much negative attention | 1 |
| - Co-morbidity of the child | 2 |
| - Follow up period considered too long | 2 |
| Complex social situations | |
| - Child in foster care | 1 |
| - Parents' divorce | 3 |
| - Psychiatric disorder in one of the parents | 1 |
| Patient (≥ 12 years of age) refuses participation | 2 |
| Negative previous experiences with participation in research | 5 |
| Planned long-term emigration | 1 |
| Unknown | 9 |




**Supplementary Figure 1.** Height standard deviation scores during follow up. Data represent means and errorbars. SDS, standard deviation score.

Supplementary Material - Reference List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