

**UK Medicines for Children Research Network (MCRN)**

**MCRN/BAPN Nephrology CSG Meeting**

**Thursday 30th April 2009; 11.00 am to 3.00pm**

**Medical Research Council Head Office, 20 Park Crescent, London, W1B 1AL**

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**Minutes**

**In attendance:**

Moin Saleem (Chair)  
Wendy Cook  
Jan Dudley  
Rodney Gilbert  
David Hughes (representing the devolved nations)  
Daniel Kirby  
Sally Johnson  
Caroline Jones  
Larissa Kerecuk (on behalf of Malcolm Coulthard)  
Ania Koziell  
Laura Pilkington  
Manish Sinha  
William van't Hoff  
Simon Waller  
Alan Watson  
Kjell Tullus

**Apologies:**

Nicholas Webb

**Welcome, Introductions and Apologies**

Moin Saleem (MS) welcomed all in attendance. Apologies were noted from Nicholas Webb and Mark Taylor.

This meeting was Daniel Kirby's first meeting with the CSG. Daniel is one of the MCRN Formulations Research Fellows and has replaced Sreenivas Pandit on the Nephrology CSG.

Daniel described the role of the Formulations Research Fellows to the group:

- They scrutinise the protocols very early on to identify potential pharmaceutical and formulation challenges in clinical trial design, ranging from:
  - Dosing accuracy
  - Safety of excipients
  - Administration volumes, accuracy and reproducibility
  - Appropriateness of formulation for the age range
  - Shelf life and in-use stability, Storage requirements
  - Compatibility with food/vehicles
  - Estimates of timelines & costs
  - Sourcing of IMPs (active/placebo) and trial packaging
  - Licensing requirements surrounding product preparation or compounding
- They also advise on investigations to be performed if appropriate; in some instances, they have the capacity to carry out such experiments, if funding is available.

## **Review of the Minutes from the Previous Meeting and Matters Arising**

The minutes from the last meeting held on Thursday 16<sup>th</sup> October 2008 were reviewed by the group. It was noted that Rodney Gilbert had been recorded under the attendance and apology list. Rodney Gilbert did attend the meeting and therefore his name should be removed from the list of apologies. The minutes were otherwise accepted as an accurate record of the discussions that took place.

## **Update from the MCRN Coordinating Centre (LP)**

The following updates from the MCRN Coordinating Centre were reported:

### Update on the Department of Health Review of the MCRN

The MCRN have recently undergone their Triennial Review with the Department of Health. As part of the documentation required for the review all CSG s were asked to report in some detail on their developments, activities and achievements over the past 18 months. **\*\*The report produced for the MCRN/BAPN Nephrology CSG was tabled at the last meeting\*\*** Elements of each CSG report were included in the main review document, which was submitted to the NIHR CRN in October 2008. This submission was followed by an interview with members of the MCRN Board and the Department of Health. The interview is believed to have gone exceptionally well with the MCRN receiving outstanding comments and many accolades for the work that the MCRN has achieved to date. The MCRN are waiting to receive an official report from the review and therefore no further information about the outcomes could be reported. Additional information will be circulated as and when it becomes available.

*ACTION: LP to circulate a copy of the review document to Moin Saleem, Jan Dudley, David Hughes and Simon Waller.*

As part of the Triennial Review, the MCRN recorded a series of clips for a DVD. The 7 minute DVD is now available as a promotional tool for people to understand more about the broad work of the MCRN. It includes various MCRN stakeholders including the President of the RCPCH, Children and Young People, Charity and Industry Representatives. The DVD can be downloaded from the NIHR CRN website (<http://www.crncc.nihr.ac.uk/index/networks/children/video.html>) and will be shortly available from the MCRN website. Hard copies can be obtained from Sarah McCauley (MCRN Training and Communications Officer) at [s.mccauley@mcrn.org.uk](mailto:s.mccauley@mcrn.org.uk).

### Feedback from the Pharmacy and Pharmacology CSG Conference

The Pharmacy and Pharmacology CSG held a conference in partnership with the School of Pharmacy, University of London (ULSOP) which aimed to aid participants in understanding the relevance of pharmaceutical research and how this can be translated into clinical studies with an emphasis on paediatric medicines. The conference took place over the course of two days (2 – 3 April 2009) and was very well attended by a number of delegates from various backgrounds including clinicians, pharmacists, pharmaceutical scientists, parent representatives, industry and regulatory affairs. Sponsorship was received gained from the ABPI, Wockhardt and Rosemount. In summary, this conference successfully highlighted the importance of translational research particularly for paediatric medicines. The CSG are very keen to publicise the success of the conference as widely as possible and they hope that an editorial piece which they have written and submitted to the Pharmaceutical Journal will be accepted. The plenary lectures and workshop presentations are available from Laura Pilkington ([laura.pilkington@liverpool.ac.uk](mailto:laura.pilkington@liverpool.ac.uk)) and will be shortly available to download from the MCRN website.

### Update on the Paediatric (Non-Medicines) Specialty Network Group

The MCRN have been asked to take a role in the coordination of the Paediatric (Non-Medicines) Specialty Network Group with the Chair of the group - Professor Anne Greenhough. The first meeting of the group will take place on Thursday 28<sup>th</sup> May and the MCRN have invited paediatric representatives from all of the Comprehensive Local Research Networks who indicated Paediatrics (Non-Medicines) to be a priority area. Also invited to this meeting are the representatives of key stakeholder groups relevant to paediatric research and the Chairs of the MCRN Clinical Studies Groups. The aim of the meeting is to clarify the role and remit of the group and to determine the most effective way to establish and support the group. A CSG Chairs Forum will take place straight after this meeting.

*ACTION: MS/LP to provide feedback from both of the meetings at the next CSG gathering.*

#### Update on Training and Education

A list of the current courses/dates for the NIHR CRN Training and Education Programme was tabled. It was noted that all courses are offered free of charge to all staff and public and, patient representatives working on or associated with the NIHR CRN portfolio of studies. Members were informed that several courses are now available online (e.g. GCP and EU Directive). Other new courses include: Patient information for parents and children (running on 5<sup>th</sup> November 2009 in Birmingham); Communication and consent in paediatric research – part 2 (running on 15<sup>th</sup> October 2009 in Bristol). CSG members were advised to contact Sarah McCauley (please email address on page 2) for further information about Training and Education.

*ACTION: Members to inform LP/Sarah McCauley of any ideas that they may have for new courses or workshops that are not being covered in the current course structure.*

#### Annual Consumer Meeting

A meeting for all of the MCRN Consumer Representatives took place on Tuesday 28<sup>th</sup> April in London. At this meeting the consumer representatives had the opportunity to discuss their role and identify ways in which it could be developed. Wendy Cook (WC) attended the meeting and found it very interactive and informative.

MS asked WC to talk about the work of NEPHCURE INTERNATIONAL that she is actively involved with. Her comments are summarised as follows: Its mission statement is to support research seeking the cause of Nephrotic Syndrome, to improve treatment and find a cure. Patient/family organisations from 8 countries are working together to explore ways to further their mutual goals in a new international patient/family organisation dedicated to meeting this mission. The group is globally connected and dedicated to searching for a cure. Their initial goals are as follows:

- To promote research in finding the cause and effective treatments for Nephrotic Syndrome.
- To advocate international co-operation of nephrologists, researchers, governments and patients.
- To locate patient organisation from other countries and encourage them to collaborate.
- To initiate and promote the need for an international biobank for Nephrotic Syndrome
- To improve the quality of life for all patients
- To encourage the standardisation of therapies for Nephrotic Syndrome.

The website is [www.NephCure-International.org](http://www.NephCure-International.org).

The group are hoping to have a meeting at the next ESPN in September. There will hopefully be as many as seven representatives from different European countries in attendance at this meeting. Unfortunately NEPHCURE USA will not be joining the meeting due to the economic turn down. The group continue to seek to collaborate and encourage researchers/doctors to work together more closely as much as possible. A Dutch doctor Jack Wetzels is hoping to do a similar initiative with adults with Nephrotic Syndrome so he looking for Nephrologists treating adults to join him.

*ACTION: WC to keep the CSG posted on all progress.*

#### MCRN Annual Conference

The third MCRN Annual Conference will take place on Thursday 19<sup>th</sup> November at the Echo Arena in Liverpool. A programme for the conference is currently being developed and the MCRN are aiming to make it as interactive and informative as possible.

*ACTION: Members were encouraged to contact LP if they had any ideas for the conference that they could assist with.*

#### **Update on Studies in Development (ALL)**

Double Blind Randomised Placebo-Controlled Non-Inferiority Trial (reviewed January 2009)

JD presented an up date to the group; a proposal was submitted to the HTA towards the end of January 2009 and the study team are waiting to hear the outcome of the application; 9/13 Nephrology Centres are in support of the trial; the study team are looking to recruit 650 patients i.e. 50 patients per Nephrology Centre (over a 2 year period); the Liverpool CTU have worked very closely on the proposal; NICE guidance has identified this topic as an important area of research; therefore the time is right to undertake such a study; the study team have applied for an MCRN research nurse for each Nephrology Centre (i.e. 13 Centres); they will be full time for the first two years and part-time there after; MS commended JD and the study team for all of their hard work; the CSG (and therefore centres) are in full support of this study.

*ACTION: JD to wait for a response from the HTA and then inform the group of the outcome.*

*Update – the study was not funded by HTA. JD is looking at options around a more limited centre study.*

#### Efficacy and Safety of Rituximab in Nephrotic Syndrome in Children and Young Adults (reviewed October 2008)

This study was presented at the last CSG meeting; [INSERT UPDATE FROM ANIA]

*ACTION: AK to circulate a copy of the revised protocol to CSG members.*

#### Does an Addition of an ARB maintain GFR in Children with CKD on ACEi? (reviewed March 2008)

KT presented an up date to the group; a proposal was submitted to the HTA in January but the study team have received no news as to whether or not they will be invited to go through to the second application stage; the trial will hopefully start in 1-2 years time subject to receiving funding; detailed feasibility data has been received from 5 centres to date.

*ACTION: KT to circulate the names of the 5 centres that have provided feasibility data to CSG members*

*ACTION: CSG members to encourage those centres who have not provided feasibility data to respond (Units can seek help from their local MCRN LRN – if necessary); KT to provide additional study information to these units*

*ACTION: KT to contact the 5 centres who have already provided feasibility data and ask them to up date their figures - if necessary.*

#### Does Taurolock compared with Heparin reduce the Incidence of Catheter related Infections in Paediatric haemodialysis catheters: a Double Blind Randomised Control Trial (reviewed March 2008)

CJ presented an up date to the group; members were thanked for the data that they provided on behalf of their unit; the study team are currently working with the MCRN CTU in Liverpool; the CTU may be wanting the team to conduct a feasibility assessment about the likelihood of recruitment and how difficult it will be to get samples; once this decision has been finalised the study team will apply for funding and the MCRN CTU will run the trial if CJ is the Principle Investigator.

#### Research into the impact of the NICE guideline CG54 on the diagnosis of renal parenchymal defects in childhood (reviewed March 2008)

AW presented an up date to the group; the study team are progressing with local funding and working through the various pit falls; the study will not be feasible in other centres unless a clinical research fellow is in post; therefore, in the mean time, the study will not be multi-centre and additional funding will not be sought.

*ACTION: This item should be removed from future agendas.*

#### CIQ Antibodies - MCGN Study (reviewed March 2008)

SJ presented an up date to the group; this is one of the first disease-specific studies to arise from the UK National Registry of rare kidney diseases and aims to build a cohort of paediatric and young adult patients with MCGN; the cohort will be the basis for basic biomedical research and translational studies; patients with MCGN are already being recruited into a smaller study of the presence of anti-C1q autoantibodies in MCGN, and this study will be incorporated into the larger cohort study as it becomes live; Study group members (last meeting 22<sup>nd</sup> April 2009) include:

**Paediatric Nephrologists**

**Adult Nephrologists**

**Pathologists**

Dr Mark Taylor  
Prof Moin Saleem  
Dr Sally Johnson  
Dr Stephen Marks

Prof Tim Goodship  
Dr Lorraine Harper  
Dr Mark Little

Prof Neil Sebire  
Prof Alec Howie  
Prof Terry Cook  
Dr Roger Malcomson

**Scientists:**

*Prof Paul Morgan and Dr Claire Harris, Cardiff*

**Components of the study:**

*Patient recruitment:* Recruitment will commence with paediatric patients through UK paediatric nephrology units and a smaller number of adult units will join once “teething problems” have been addressed. This will be facilitated by liaison with the adult nephrology (glomerulonephritis) CSG.

*Clinical Information:* The cohort data will be web based and hosted/supported by the Rare Disease Registry. The website is in advanced stages of planning.

*Clinical samples:* DNA for complement gene mutation analysis will be sent to Prof Tim Goodship, Newcastle. Serum for biomarkers/functional complement analysis will be sent to Prof Paul Morgan. Pathology specimens will be reviewed by the expert pathology panel.

*Treatment trials:* The group will approach Alexion to propose a treatment trial with Eculizumab.

**Ethics/R&D:**

The initial phase of the study (anti-C1q antibodies) has ethical approval for recruitment from all UK paediatric nephrology units. Local R&D approval has been problematic. The group will seek CSP (central sign off) for the next phase of the study, but local units should continue to seek R&D approval so that recruitment is not delayed.

**Funding:**

The cohort development is funding by a substantial grant from the MRC. Individual aspects of the study (e.g. genetics) will seek additional funding.

*ACTION: Members to continue to seek local R&D approval and inform Mark Taylor of progress*

*ACTION: Members to recruit patients as soon as R&D approval gained*

*ACTION: Members to send samples as documented in the study protocol as soon as patients have been recruited*

*ACTION: LP to send information about the Coordinated System for Gaining NHS Permission (CSP) to SJ*

Vitamin D (ergocalciferol) Supplementation in Children with Early Chronic Kidney Disease – a Multicentre, Randomised, Double-Blinded, Placebo-Controlled Study (reviewed March 2008); also known as the ACHIEVE Study.

WVH presented an up date to the group on behalf of Dr Rukshana Shroff; a preliminary application was submitted to the NIHR Efficacy and Mechanism Evaluation (EME) programme and has been shortlisted by the EME Board; a full proposal has now been submitted; other possible sources of funding include Action Medical Research (AMR) and Kids Kidney Research (KKR); if funding from the NIHR is achieved then a clinic at University College London Hospital (UCL) will be used to run the study; 7 centres have signed on to date; these include Great Ormond Street (GOSH), Nottingham, Bristol, Leeds, Manchester and the Evelina Children’s Hospital; the study is still open to other centres; minor changes to the protocol have been made (MS is in receipt of the revised version); 44 children from GOSH have been screened, which resulted in 18 children being allocated to the trial (NB. there was one drop out; the child did not like the taste of the tablet); an important change to the study has been made; the study team are not aware of the vitamin D levels; a pharmacist and a data monitoring team are being used; if the level exceeds the range then the data monitoring team will inform the study team and the child will be un-blinded from the study; multiple safety parameters are in place; this study is not a portfolio study at the moment but once funding has been obtained it will be submitted for adoption; all sites should have received a copy of the update to protocol (MS reported that he had not received this copy).

*ACTION: WVH to ask Rukshana to circulate the protocol to members/centres again*

*ACTION: Members/centres to respond to Rukshana directly with any specific needs*

## **Update on Funded Studies (ALL)**

### Nephrotic Syndrome

MS informed members that he had not received an update from NW.

*ACTION: MS to contact NW and to keep the group up to date with any progress.*

### Rare Disease Registry (RADAR)

MS presented an up date to the group; this study has been funded by an MRC Programme Grant; the purpose of the National Registry of Rare Kidney Diseases (now designated RaDaR, Rare Disease Registry) is to facilitate translational and epidemiological research into rare kidney diseases in children and adolescents by setting up and maintaining comprehensive clinical databases in partnership with disease-specific research groups; it is a UK multi-centre trial and has been recently adopted by the MCRN; the registry will be Web-based and data will be encoded and held on a secure server; data entry will be made by the clinician with responsibility for the patient usually their nephrologist or paediatric nephrologist; patients who have consented to participate in the registry will have their own user name and password that allows them to see their own data file, to enter data fields themselves, and to receive information about their clinical condition; parents and guardians of children who participate in the registry will have similar access until such time as the patient is mature enough to consent for himself or herself, and the right of access is transferred from parent or guardian to the patient; the data from the registry will be made available to researchers investigating specific rare diseases in accordance with the RaDaR operating policy; a web-designer has been employed and a workable version of the webpage will be ready for members to comment on shortly; ethics are being finalised; it was noted that there is an international perinatal registry that pays you for registering patients and there is an incentive for the more patients you register the higher your name will go in the publications; MS informed the group that any recruitment for RADAR will be suitably acknowledged in a publication.

## **Other Studies**

### Quality of Life Study

AW presented an up date to the group; a questionnaire has been developed to audit the Quality of Life (QOL) of children with chronic renal disease in order to explore the impact of treatment modality. It has been tested on a local population and has been published (please see attached). AW would like to roll the questionnaire out into other centres; funding was not obtained from the RFPB; Evelina Children's Hospital, Bristol and Newcastle are keen to use it; each Nephrologist to speak a psychologist in their unit to make the survey work; Their name will be on a paper (members to inform AW in an email); this = an MCRN/BAPN audit.

## **Industry Approaches (ALL) – [www.clinicaltrials.gov.uk](http://www.clinicaltrials.gov.uk)**

### Alexion Trials:

Studies adopted over the last few days:

MCRN040 Alexion - Eculizumab/adolescents with PT-resistant aHUS (SD063/CCRN31)

MCRN041 Alexion - Eculizumab/adolescents with PT-sensitive aHUS (SD089/CCRN061)

LRNs: GMLC (1), SENCE (2), SW (1), CMNW (1), T (1) + WM (1)? and CLRN: NTW (1) +; looking for more interested centres.

William van't Hoff represented MCRN on the CCRN adoption committee and made the following comments:

“The committee wanted to highlight that these forms of atypical HUS occur in very young children who are excluded from these protocols. In addition, our paediatric nephrologists indicated that the screening criteria are extremely tight for the inclusion of older children.”

Alexion response:

“Alexion is very aware of the need to perform studies in paediatric patients and is working presently to design a protocol. It is anticipated that a paediatric study will also begin in 2009.

The inclusion criteria have been designed to get a clear understanding of the patient's profile, in particular the impact of plasma therapy prior to treatment with the investigational drug. In the event that the drug proves efficacious it is likely that further clinical trials will be required and the inclusion criteria may be different.

We feel this is the appropriate design for the current studies and that they should not be altered, particularly as they are part of a multinational programme which has commenced elsewhere. However we would very much welcome the thoughts of the paediatric haematologists on how the inclusion criteria could be less tight to help inform future work"

Alexion have agreed to a set up fee of £1500 with no expectations of recruitment.

For more information on the Alexion trials please go to the following links:

<http://www.clinicaltrials.gov/ct2/show/NCT00844844?term=eculizumab+AND+adolescents&rank=2>

<http://www.clinicaltrials.gov/ct2/show/NCT00844428?term=eculizumab+AND+adolescents&rank=3>

*ACTION: Members to feed back expressions of interest to MS*

*ACTION: MS to feed this information back to Andrew Rose at the Coordinating Centre*

*ACTION: LP to find out if all CSG members have got CDAS in place – when this has been confirmed LP to ask AR to circulate a copy of the full protocol to members*

Micera ESA Anaemia (Phase II) Study

MS got approached by a company to undertake a feasibility assessment for the above study. The following questions were circulated to CSG members:

- Roughly how many children with CKD are being treated in your unit in a year?
- Roughly how many of those children are under the age of 5?
- What percentage of the children being treated with ESAs in the age categories 0-5 years, and 5 to 17 years?
- Can you give a rough estimate of the number of children who might agree to take part in a clinical trial of a new long-acting ESA?
- What ESAs are being used in your unit?
- Who decides which ESA should be used, and what information are those decisions based on?
- Are frequent SC injections an issue?
- Do you have any other issues with ESAs in children?
- 

4 out of 13 centres have provided data for the above questions (i.e. from Nottingham, Newcastle, Liverpool, Glasgow and Bristol). MS has collated the responses received to date and has sent this information to Andrew Rose. The group discussed the study and agreed to support the initiative; all units who have not responded agreed to provide some idea of numbers, enthusiasm etc following the meeting.

Discussion about feasibility requests led to a discussion about feasibility assessments being more realistic/accurate. CSGs and LRNs should work together to look at past experiences of recruiting to studies and extrapolate the data up. This approach was commended by members.

*ACTION: MS to provide feedback to the company through Andrew Rose*

*ACTION: MS to find out from AR if this study is running in the UK and if it is open*

*ACTION: If open – go back to centres who haven't responded and those centres who have responded and ask if they want to edit their responses*

*ACTION: MS to send questionnaire around again*

*ACTION: MS to check with AR if members can see the protocols as the eligibility criteria would be helpful*

*ACTION: MS to let AR know about the additional comments raised from the discussions and AR will feed this information back to the company*

## **Current Calls for Funding (LP)**

For funding opportunities relevant to medicines for children please go to: <http://www.rdfunding.co.uk/specialEdition/SE.asp?ID=58>

**ERA- NET** – the aim of the ERA-NET call is to stimulate trans-national, collaborative proposals. It is currently expected that applications should involve a minimum of three research groups from at least two different member states. Applications will need to demonstrate the added value of collaboration. The broad topics for the call are: The development and use of innovative methodology in medicines for children research and Innovation of paediatric formulations and drug delivery systems. More detailed information should hopefully be available in late May. The ERA-NET Partners anticipate the call being published in Mid-September with a deadline for outline proposals/letters of intent at the end of October. \*\*LP tabled a document that contained a list of the priorities that reached consensus for all of the subject specific surveys including nephrology & urology\*\*

**HTA** – The HTA has a proud record of commissioning research in important clinical areas that improve the management of patients within the NHS. The government has increased the funding for research and is welcoming suggestions for areas of research from professional organisations and, in particular, speciality groups or special interest groups. They have asked for groups to state the following:

- **Identify a clear research question**
- **Specify the population of patients that you wish to study**
- **State the drug that you wish to investigate including the comparator (this may or may not be a drug)**
- **State both primary and secondary outcomes**

Imti Choonara (Chair of the HTA Pharmaceutical Panel) is happy to receive such a proposal which he will then discuss and evaluate with members of the HTA. Thereafter, it will be discussed by members of the pharmaceutical panel. If there is widespread support for the proposal, the proposal will be advertised as a commissioned area of research within one year and investigators would be encouraged to apply for funding.

Suggestions can range from systematic reviews to clinical trials.

### **Any Other Business**

CJ mentioned an audit that she had received looking at rare diseases; MS has forwarded it to the Chair of the BAPN. Meeting papers to be circulated prior to 1 week.

### **Date, Time and Place of Next Meeting**

The next meeting will take place in approximately 6 months time. Dates will be circulated shortly.