

## Renal Association Clinical Trials Committee Meeting

Friday 16th January 2009; CTSU; Oxford

### Minutes

#### Attendees:

Jo Adu; Colin Baigent (Chair); Tanaji Dasgupta; Lorraine Harper; Richard Haynes; Neil Iggo; Natalie Ives; David Jayne; Phil Kalra; Martin Landray; Chris McIntyre; Matt Morgan (SpR Club Representative); Albert Ong; Kazem Rahimi; Christina (Kirsty) Reith (Minutes); Richard Sandford; Caroline Savage; Keith Wheatley

#### Apologies:

Rob Preston; Moin Saleem; David Wheeler

#### Agenda

1. Approval of minutes from last RACTC meeting (25<sup>th</sup> January 2008)
2. Special Topics Briefing: SHARP - current status and future plans
3. Integration with UKCRN and UKKRC
4. Update on Planned Trials
  - Dialysate Cooling Study
  - UK-REN-1/BOND trial
  - 3C trial
  - APKD study
  - FAVOURED study
  - PEXIVAS trial
  - Eculizumab in a HUS
  - Vitamin D replacement in stage 3B/4 CKD
5. Review of Trial Progress
6. UK Nephrology Trials Meeting
7. AOB

### 1. Approval of minutes from last meeting (25<sup>th</sup> January 2008)

There were no comments in relation to the minutes from the 25<sup>th</sup> January 2008, and so these were considered approved.

### 2. Special Topics Briefing: SHARP – current status and future plans

Martin Landray (SHARP Clinical Coordinator) presented an update on the Study of Heart And Renal Protection (SHARP). This talk included a summary of SHARP's baseline characteristics and highlighted the challenge of maintaining compliance. There was discussion as to how to learn from the methods used to try to improve compliance in SHARP in order to advise future studies. In terms of study power, it was noted that the LDL difference at ~ 2.5 years is 0.9 mmol/l and thus in line with expectations, and that the event rate for the primary end-point is on track. However, this comes with the caveat that events/outcomes are currently unadjudicated and experience from 4D and CORONA indicates that not all cardiac deaths may be amenable to lipid-lowering. It was noted that event outcomes will be ONS-tracked in the UK, but such tracking worldwide may be more difficult due to different systems in place.



SHARP Talk for  
RACTC January 2009

### 3. Integration with UKCRN and UKKRC

Caroline Savage updated the RACTC on the UK Kidney Research Consortium (UKKRC) and UK Clinical Research Network (UKCRN) Renal Speciality Group as per the attached

document. The importance of growing and increasing the strength of the UKKRC so as to promote translational research in nephrology was highlighted. It was clarified that if KRUK funds a renal study, that it will automatically be adopted onto the UKCRN portfolio, and hence will be able to receive support through the UKCRN network.

There was discussion as to whether to arrange a meeting for all UKCRN renal leads (including devolved nation renal leads) and all UKKRC renal contacts so that all relevant parties are briefed on matters pertaining to renal trial activity. This was seen as particularly important in ensuring that there is a unified renal voice in the eyes of the UKCRN, whose focus is often on accrual numbers and recruitment as opposed to long-term follow-up and compliance in trials, which often presents an equal challenge. By having a unified body, it should be possible to identify evidence gaps in renal medicine and work towards filling them through an evolving pipeline of renal studies/trials.



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Caroline Savage highlighted the Renal Trials tracking spreadsheet (on the RA web-site as created by Kirsty Reith) as a way in which renal trial activity can be promoted. Lorraine Harper suggested that it would be a good idea to develop renal sub-speciality focus groups so as to more effectively identify where the evidence gaps are, and thus prime/facilitate the entry of renal studies into the UKCRN trials portfolio. Rheumatology has already effectively used this model with good success, and some such speciality sub-groups are already in place in nephrology e.g. dialysis and cardio-renal groups. The RACTC decided that the focus groups should be as follows:

- (i) Bone/phosphate: suggested lead David Wheeler (Royal Free)
- (ii) Transplantation: suggested leads Peter Friend (Oxford) and Alan Salama (Hammersmith)
- (iii) Dialysis: suggested leads Chris McIntyre (Derby) and Ken Farrington (Lister Hospital, Stevenage)
- (iv) Cardio-renal: suggested lead Phil Kalra (Salford)
- (v) Acute Kidney Injury: suggested lead Andrew Lewington (St James's Hospital, Leeds)
- (vi) Glomerulonephritis/vasculitis: suggested lead Lorraine Harper (QE, Birmingham)
- (vii) Cystic Kidney Disease: suggested lead Richard Sandford (Cambridge)
- (viii) CKD progression and biomarkers: suggested lead Paul Cockwell (QE, Birmingham)

Caroline Savage highlighted the importance of these groups including paediatric representation.

It was agreed that Colin Baigent and Caroline Savage will co-draft a letter on behalf of the UKKRC to these proposed sub-speciality leads, asking them to form focus groups with a view to identifying the relevant evidence gaps and bringing trial proposals to the next RACTC meeting (which is likely to be in early July; exact date TBC).

#### **4. Update on Planned Trials**

Talks were presented in relation to several proposed trials as summarised below:

##### **Dialysate Cooling Study**

Chris McIntyre updated the RACTC on a proposed randomised prospective controlled pilot study looking at the effect of dialysate cooling on myocardial ischaemia (as evaluated by cardiac MR) in incident HD patients. This will be a study based in the Midlands (including Derby, Stoke, Birmingham Heartlands and Leicester) and aims to recruit approximately 200 patients within 90 days of commencing HD. Patients will be randomised to either normal/usual care dialysate, or cooled (effectively non-warmed) dialysate. Two renal trainees have been recruited to do PhDs and work on this study and will commence work on this imminently. The aim is to recruit the first patient by March 2009. There have been some issues obtaining funding; the study proposal is currently with the NIHR. There may be a possibility of factoring dialysate cooling into the design of the main phase UK-REN-1/BOND study in the future.

### **UK-REN-1/BOND study**

Kazem Rahimi gave an update on the UK-REN-1 study. The study acronym may change to BOND (Beta Blockers and Outcomes in Nephrological Disease). A questionnaire was circulated to Renal Association consultant members in 2008, and the results from this (attached) indicate that there is good support for doing a trial of beta blocker therapy in renal patients. He explained that there have been problems obtaining a supply of beta blocker, and more particularly matching placebo, and thus some funding issues. This has led to a change in tack, such that in contrast to the initial plan of having a pilot study and then a main study, it is now anticipated that there will just be a main study which may be an open-label study as opposed to a placebo-controlled trial. In order to decrease potential bias in using such an open label design, the plan is to avoid using subjective outcomes e.g. the primary outcome is likely to be cardiovascular deaths as assessed by a blinded end-point committee. By identifying non-fatal events through registries (e.g. HES), bias can be avoided (because whether an event is reported to HES will not depend on study treatment allocation).

Peter Weissberg (BHF Medical Director) has indicated that the BHF is willing to consider a funding application. In tandem, industry funding/drug supply is still being pursued. The importance of such a planned large scale study receiving adequate resources was highlighted, along with the need for KRUK/UKKRC and thence UKCRN support i.e. collaborative working/funding should reduce the cost for any one funding body and make such a trial more likely to be a success.



K:\rsg\UK-REN-1\  
Questionnaire\Reply



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### **3C Study**

Richard Haynes gave an update on this proposed randomised trial of Campath-based induction therapy versus standard care for renal transplant recipients, with a comparison of sirolimus-based maintenance therapy versus tacrolimus-based maintenance therapy. The protocol has now been agreed by the 3C Steering Committee and many UK centres have expressed an interest in participating in the study. There is also a possibility of including some centres in the Netherlands. Funding will be obtained from 2 (possibly 3) pharmaceutical companies. The study is anticipated to commence in summer 2009 with a target of 800 participants. It was suggested that the study could look at long-term outcomes from the induction comparison as it might not be biased by the maintenance randomization. Richard explained that the hope was to do this, but that long-term outcomes were not the primary outcome because this comparison is potentially biased if unequal proportions go forward to the second randomisation from the Campath and Basiliximab arms.



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### **APKD study**

Richard Sandford presented a proposal to conduct a pilot study of high fluid intake (step-wise increment up to 4 additional litres of fluid over normal intake per day) in ~ 40 healthy volunteers with a view to this extending to a study in AKPD patients. MREC approval is being sought for the pilot study and it is hoped that it will commence in ~ 4 months time. The RACTC agreed that APKD patients are generally a very engaged and interested group and therefore that such an intervention may well be tolerated. Such a main study could be a parallel design with an end-point of rate of change in kidney volume, but a cross-over design and an end-point of absolute change in kidney volume were also discussed. The issue of controlling for people decreasing their normal fluid intake was considered, as was whether it would be better to use an isotonic fluid for fluid intake as opposed to water. The question as to whether it would be appropriate to screen participants for AKPD genotype so as to discriminate PKD 1 and PKD 2 patients in the main study was raised, given that these 2 groups of patients have different phenotypes/behave differently. It was noted that genotype

should not alter study power in this context, and that it may be better to simply randomize patients and then retrospectively genotype if so desired.



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### **FAVOURED study**

Colin Baigent presented some slides on behalf of Ashley Irish (Australasian Kidney Trials Network) in relation to a proposed study called Fish oil and Aspirin in Vascular access Outcomes in RENal Disease (FAVOURED study). The Australasian Kidney Trials Network is looking for a UK Collaborator, and Colin asked if there were any interested parties (including renal SpRs) in working on this trial as a joint project. The position of the joint collaborator (e.g. whether they would be listed a co-investigator/be on the study's writing committee) would largely depend on the collaborator's degree of involvement and success of UK recruitment.

Chris McIntyre expressed an interest in being involved in a large, collaborative renal dialysis access study, but wondered whether FAVOURED may be difficult to take forward in the UK partly because of different surgical access procedures in the UK from Australasia. However, FAVOURED may differ from previous trials in this respect because participants are randomised before the surgical result of the fistula formation is known.

It was agreed that Colin Baigent will send Chris McIntyre the FAVOURED study protocol and Chris McIntyre will then take this proposal to the Dialysis Focus Group to seek interest. In addition, Matt Morgan (SpR Club representative) is to be forwarded the FAVOURED slides so as to present them at the SpR club meeting to be held in Sheffield in February 2009 to gauge any potential SpR interest.

### **PEXIVAS study**

David Jayne updated the RACTC on this 2x2 factorial blinded international randomised controlled trial of glucocorticoids and plasma exchange in ANCA associated vasculitis. This study is being run in conjunction with the Birmingham Trials Unit, and mechanistic studies are to be run in parallel with this study. It is hoped that the CRF will be electronic as opposed to paper-based. There was discussion surrounding patient survival in relation to GFR since older patients tend to present with a higher GFR, and this could potentially be a confounding factor. There is currently a delay in the trial's progression due to FDA and pharmaceutical interest but this issue is being actively pursued. There have also been issues raised in relation to source data monitoring following a more general (i.e. not PEXIVAS specific) MHRA-inspection of Addenbrooke's Hospital. It was suggested that the PEXIVAS group could suggest to the hospital trust/MHRA that remote statistical monitoring can be a more effective way of monitoring a study, and would help circumvent this problem. The PEXIVAS group were congratulated by the RACTC on their achievement to date.

### **Eculizumab in aHUS**

The attached summary was included in the RACTC meeting pack. This study is recruiting and looking for interested parties to act as participating centres. It was agreed that the RACTC web-site would be a good place to promote actively recruiting trials such as this who are looking for collaboration.

Caroline Savage offered to liaise with Tim Goodship for further details on this study to go on the web-site; she will then forward these to Kirsty Reith so they can be uploaded.



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### **Vitamin D replacement in stage 3B/4 CKD**

The attached summary was included in the RACTC meeting pack. The Committee agreed to read through this proposal and forward any comments to Colin Baigent who can then feed back any comments to Ed Lamb (St Helier).



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## 5. Review of progress in ongoing trials

### **ASTRAL**

Phil Kalra updated the Committee on progress with ASTRAL. Recruitment was completed in October 2007 and 12 month follow-up was thus completed in October 2008. The ASTRAL results were initially presented in March 2008, and have been widely publicised including being presented at the ACC, ASN, ERA-EDTA and in Australia-New Zealand. The draft ASTRAL manuscript is nearly finalised having undergone wide review. An additional grant has been provided by KRUK for an extra 3 years of follow-up, meaning that each patient will be followed up for 4-5 years. It is anticipated that the ASTRAL group will go on to do a meta-analysis with other similar groups such as the CORAL investigators. The RACTC congratulated the ASTRAL team on their achievement.

### **Membranous nephropathy trial**

This is now fully recruited and a report is anticipated in 2009.

### **MERIT myeloma trial**

This trial of adjunctive plasma exchange in patients with newly diagnosed multiple myeloma and acute renal failure has unfortunately had to close due to recruitment problems (~ 80 patients recruited out of target of ~ 280).

### **Renal trial tracking spreadsheet**

Kirsty Reith has updated the spreadsheet she created summarising renal trial activity in the UK. This can be accessed through the RA web-site as follows:

<http://www.renal.org/pages/pages/academic-affairs/trials/trial-information.php>

It was explained that the spreadsheet details randomised trials but not prospective or observational studies. Spontaneous feedback of ongoing renal trial activity through the web-site has been poor, but the database has greatly expanded since Caroline Savage wrote to UK CLRN renal leads asking them to disseminate the spreadsheet to local renal units and to then feed back local renal trial activity to Kirsty accordingly. It was noted that there had been very good feedback from some units but that the information had been more difficult to obtain from others. It was agreed that the devolved nation renal leads should be approached in a similar manner to get as comprehensive a picture of UK nephrological trial activity as possible. The RACTC were asked to check the spreadsheet, and to inform Kirsty of any relevant updates or trials that had been missed off the spreadsheet. Kirsty will upload the updated version of the RACTC tracking spreadsheet to the RA web-site in the next month, and ask Mark McGregor to highlight the updated RACTC web pages in the main RA web-site 'news' section. Kirsty will liaise with Caroline Savage in relation to ensuring that the devolved nations are also represented.

## 6. UK Nephrology Trials Meeting

The CTC discussed the possibility of hosting a future Nephrology Trials Meeting in Oxford. It had been hoped to host this in 2009, but it was agreed that February 2010 would be more appropriate. It is thought to be important that such a meeting should have a varied programme aimed at both consultants and SpRs, so as to encourage future career development encompassing renal trials.

## 7. AOB

The annual RA/BTS conference in Liverpool in April 2009 has scheduled a 90 minute slot for a joint UK Renal Registry/RA Clinical Trials Committee session. Colin Baigent will liaise with the UKRR in relation to the format for this session. The RACTC were reminded that posters in relation to trials for the RA/BTS conference can be directly approved by the RACTC, as

## January 2009 RA CTC Minutes

opposed to having to go through the central process. It was therefore agreed that all of the speakers who had presented a trial at the RACTC meeting (see section 4 above) should submit a poster. It is thus hoped that a section of the posters at the conference can be dedicated to renal trials and hence raise the profile of trial activity in the nephrological community.

### **Next CTC Meeting:**

A RA CTC was scheduled for September 2008, but this had to be cancelled due to too many Committee members having other commitments. It was agreed that the RA CTC should aim to meet twice per year in the future, with the next meeting being in ~ July 2009; exact details to be confirmed.

### **Summary of action points:**

<b>Action</b>	<b>RACTC member(s)</b>
Draft a letter on behalf of the UKKRC to proposed renal sub-speciality leads, asking them to form focus groups with a view to identifying relevant evidence gaps and bringing trial proposals to the next RACTC meeting	Colin Baigent Caroline Savage
Colin Baigent to send Chris McIntyre the FAVOURED study protocol; Chris McIntyre to then take this proposal to the Dialysis Focus Group to seek interest. Matt Morgan (SpR Club representative) to be forwarded the FAVOURED slides so as to present them at the SpR club meeting to be held in Sheffield in February 2009.	Colin Baigent Chris McIntyre Matt Morgan
Caroline Savage to liaise with Tim Goodship regarding further details on the Eculizumab and aHUS study to go on the RACTC web-site; details to then be forwarded to Kirsty Reith so they can be uploaded.	Caroline Savage Kirsty Reith
Read through vitamin D replacement in stage 3B/4 CKD proposal and forward any comments to Colin Baigent.	All
Check details on renal trials spreadsheet and convey any changes/additions required to Kirsty Reith.	All
Update RA CTC web-site details and ensure RACTC mentioned in next RA e-news page. Upload updated renal trials spreadsheet onto CTC web-site. Ensure that actively recruiting trials are promoted on the RA web-site. Liaise with Caroline Savage in relation to ensuring that devolved nations are also represented.	Kirsty Reith
Liaise with the UKRR in relation to the format for the joint RACTC/UKRR session at the Liverpool April 2009 RA/BTS conference.	Colin Baigent
RACTC meeting speakers to prepare a poster for submission to the joint April 2009 RA/BTS conference	Chris McIntyre Kazem Rahimi Richard Haynes Richard Sandford David Jayne
Arrange date for next CTC meeting.	Kirsty Reith