PROPOSAL FROM THE RENAL COMMUNITY FOR THE DEVELOPMENT OF CLINICAL RESEARCH IN KIDNEY DISEASES THROUGH A UK KIDNEY RESEARCH CONSORTIUM USING THE COMPREHENSIVE RESEARCH NETWORKS IN THE UK

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on behalf of the Renal Association, Kidney Research UK

and the British Association of Paediatric Nephrology

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I: The case for clinical research in kidney disease

Introduction

The kidneys perform several essential body functions including excretion of waste metabolites, salt and water balance, regulation of haemoglobin production, and calcium and phosphate balance. Kidney damage can occur due to either acute or chronic insults, leading to acute renal failure (ARF) with a temporary decline in kidney function or chronic kidney disease (CKD) where kidney function is permanently compromised.

The Burden of Kidney Disease

a) Chronic kidney disease

The most important renal manifestation of CKD is end-stage renal disease, also called established renal failure (ERF). Here the kidney damage is so severe and irreversible that death is inevitable without some form of renal replacement therapy (RRT), either by dialysis or kidney transplantation. Such treatments are expensive as they are lifelong and resource intensive. As in all developed countries, the RRT programme in the UK has increased steadily over the last two decades. One metric is the ‘acceptance rate’, which is a function of the incidence of ERF, and the patterns of detection, referral to nephrology services and commencement on RRT. This rate has risen from 65pmp in 1991/2 to an estimated 100 pmp in 2003 (1). The prevalence of RRT is now over 600 pmp (approximately 37000 patients in the UK) and is projected to rise to over 1000 pmp over the next two decades, at an NHS cost of over £2 billion (2). South Asian and African-Caribbean ethnic minorities have increased acceptance rates, associated in part with increased rates of type 2 diabetes and also with faster progression of CKD to ERF. Rates are greater in areas of deprivation, consistent with CKD being associated with lower socio-economic status.

The vast majority of patients who develop ERF have underlying CKD which has progressively worsened. This has highlighted the importance of primary prevention of CKD and its major determinants in at-risk populations, including those with type 2 diabetes, obesity, and hypertension, the origins of which can often be traced back to childhood and early adult life. Early detection of CKD is essential to allow interventions to prevent progression (secondary prevention). Hitherto recognition of CKD was hampered by use of the simple but insensitive measure, serum creatinine (3). The US KDOQI have developed a new classification scheme for CKD based on assessment of glomerular filtration rate (GFR), the best overall measure of kidney function (4) (Table 1). This can be estimated by formulae which adjust serum creatinine for factors affecting creatinine production such as age, gender and ethnicity. In 2006, one such formula, the Modification of Diet in Renal Disease (MDRD) formula was adopted nationally in the UK as the standard method of reporting renal function by NHS pathology laboratories (5). As GFR falls, the complications of CKD appear and worsen (anaemia, disturbances in parathyroid hormone and calcium/phosphate balance, metabolic acidosis, secondary hypertension, and increased cardiovascular risk) with consequent effects on quality of life becoming apparent especially at CKD stage 3 and beyond (6). Of particular relevance is the emerging evidence that CKD (including stage 1 and 2) is an independent risk factor for cardiovascular disease, and that the main outcome of early CKD is not progression to ERF but premature death from cardiovascular disease. CKD is a cardiovascular risk factor as powerful as diabetes.
Table 1: Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage of CKD</th>
<th>GFR ml/min/1.73m²</th>
<th>Other criteria</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>&gt;90</td>
<td>Additional evidence of kidney damage, e.g., proteinuria</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Additional evidence of kidney damage</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td></td>
</tr>
<tr>
<td>5 (ERF)</td>
<td>&lt;15</td>
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</table>

Population health surveys in adults have highlighted the high prevalence of CKD in adults in developed countries. The best known and most widely quoted is the 1988-94 NHANES III survey in the USA, where nearly 5% of the adult population were estimated to have CKD stage 3-5 and overall, around 11% of the population had some evidence of kidney disease; the Ausdiab study provided similar information (7, 8).

There has been no nationally representative population survey in the UK. A recent study using GP computer data in 12 practices, with MDRD GFR estimation, showed a prevalence of about 5% with known GFR <60, although this could be higher if the data were extrapolated to the untested population (9). The obesity and type 2 diabetes 'epidemic' in the UK is likely to increase the incidence of CKD, and reduce the age at which it occurs.

b) Acute renal failure

The epidemiology of acute renal failure (ARF) is less well documented than chronic kidney disease, the reported incidence depending on the definition used and the population studied (10-13). ARF is often multifactorial especially in the elderly. With the expansion of complex surgery to older patients with more comorbidity, who often have pre-existing reduced kidney function and/or vascular disease, post operative ARF is increasingly common (10). ARF is also an important complication in critically ill hospitalised patients on intensive therapy units with multi-organ dysfunction, especially when accompanied by sepsis (6). Both situations have high mortality and/or prolonged hospital stay. Indeed, a recent meta-analysis indicated that the mortality from ARF has remained unchanged over the last 30 years, representing a significant opportunity for improving care of these patients, which is currently associated with high costs to the NHS (14).

There is an ongoing research need to identify better ways of preventing ARF and managing severe ARF once it occurs.

c. The kidney in systemic disease

The kidneys are frequently involved as part of a more generalised, or systemic, disease process. This occurs in infections, such as hepatitis B, C and HIV, malignancies, such as myeloma and lymphoma, and autoimmune disorders, including systemic lupus erythematosus and vasculitis. Kidney involvement frequently confers an adverse prognosis in these conditions, and together they account for 10% of the causes of ESRD. Because progression of renal disease is often preventable it is particularly important that appropriate research is targeted to improving their detection, identifying
patients at an early disease stage and improving the current therapeutic and monitoring strategies.

**Need for clinical and epidemiological research in renal disease**

The Academy of Medical Sciences report, Strengthening Clinical Research (http://www.acmedsci.ac.uk), provided a compelling argument to enhance capacity for experimental medicine and translational research in the UK, where these terms covered the following:

**Table 2: The Scope of Translational Medical Research**

<table>
<thead>
<tr>
<th>Experimental medicine studies</th>
<th>Clinical trials and population based studies</th>
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</thead>
<tbody>
<tr>
<td>Proof of concept studies</td>
<td>Disease networks</td>
</tr>
<tr>
<td>Early phase (I and II) studies</td>
<td>Late phase (III) clinical trials</td>
</tr>
<tr>
<td>Evaluation of novel diagnostic methodologies</td>
<td>Drug and disease monitoring</td>
</tr>
<tr>
<td>Characterisation of intermediate phenotypes or surrogate markers for disease</td>
<td>Classical epidemiology, Genomic epidemiology</td>
</tr>
<tr>
<td>New technologies and technology assessment</td>
<td>Health services research</td>
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</table>

Many of these areas are already represented by current studies being undertaken by the renal community (see below), but there are still important themes which have yet to be addressed systematically. These include the true prevalence of CKD, the lack of good markers for rates of disease progression, how best to detect early CKD, and the extent of the links between CKD and cardiovascular disease.

Kidney disease has been the focus of a National Service Framework for England, published in 2004 and 2005, that has provided realistic guidelines for improving health care delivery to kidney patients. Kidney disease is fortunate to benefit from the setting of national standards for clinical care through the aegis of the Standards Committee of the Renal Association. The implementation of evidence based renal standards and comparative audit by the UK Renal Registry and UK Transplant are important tools to improve the quality and outcomes of dialysis and transplantation. An expansion of the Renal Registry to monitor CKD through its five stages would enable the health burden of early disease (Stages 1-3) to be monitored, including its impact on cardiovascular risk.

Kidney disease research has received far less support than, for example, cancer and heart disease. This partly reflects the previously perceived low incidence and prevalence of kidney disease, which is a misplaced concept as already outlined. Kidney disease has also suffered from a lack of substantial charity funding compared to some other disorders, since the main charitable organisation, the National Kidney Research Fund, recently re-named Kidney Research UK (KRUK), has a research funding budget of <£3 million per annum.
II: Strengths and achievements of kidney research in the UK

Current clinical kidney research capacity

The renal community are already actively participating in many of the areas identified in the report from the Academy of Medical Sciences, as illustrated here:

Table 3: Examples of current clinical research in the renal community

*Pharma = funded by pharmaceutical industry

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples from the Renal community*</th>
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<tbody>
<tr>
<td>Proof of concept studies</td>
<td>ACTIVE (Pharma)</td>
</tr>
<tr>
<td>Early phase (I and II) studies</td>
<td>RITUXVAS (Pharma); Taurolidine dialysis catheter study UKATT, AL Amyloid (CRUK)</td>
</tr>
<tr>
<td>Characterisation of intermediate phenotypes or surrogate markers for disease</td>
<td>Vascular calcification study (KRUK and Pharma)</td>
</tr>
<tr>
<td>New technologies and technology assessment</td>
<td>Satellite unit haemodialysis (HTA Report); Home dialysis (NICE Report)</td>
</tr>
<tr>
<td>Disease networks</td>
<td>EU CRF network; European Vasculitis Study Group (EUVAS)</td>
</tr>
<tr>
<td>Late phase (III) clinical trials</td>
<td>ASTRAL (MRC, KRUK and Pharma); MERIT (Leukaemia Research Fund and Cancer Research UK); SHARP (Oxford Clinical Trials Unit); Treatment of Membranous nephropathy (MRC and KRUK); IMPROVE (organised by EUVAS with Pharma); Steroid treatment of nephrotic syndrome in children (KRUK)</td>
</tr>
<tr>
<td>Genomic epidemiology</td>
<td>Glomerulonephritis DNA collection (MRC and KRUK); Vesicoureteric reflux DNA collection (Wellcome Trust &amp; KRUK).</td>
</tr>
<tr>
<td>Health services research</td>
<td>ABLE (KRUK); Overlap with 2 technology assessments above</td>
</tr>
</tbody>
</table>

• *Brief descriptions of each of these studies are available in the Appendix.
• Funding bodies or organising agencies in brackets.

The UK renal community has a strong record of collaborating internationally (e.g. EUVAS; EU CRF network; SHARP - an international Study of Heart and Renal Protection organised by the Clinical Trials Support Unit, Oxford) and engages with other specialist societies to promote studies in specific areas (e.g. MERIT is a trial in multiple myeloma, organised jointly by the Renal Association and UK Myeloma Forum/British Society for Haematology with funding from Leukaemia Research Fund and Cancer Research UK). The Clinical Trials Committee of the Renal Association has initiated the Immunosuppression in Progressive Membranous Nephropathy trial, receiving substantial support from the MRC and KRUK. Collaborative funding has been instituted for several studies, e.g. triple support from MRC, KRUK and industry for ASTRAL (a trial of non-invasive therapies versus stenting for renovascular disease). The current portfolio includes studies on rare as well as common conditions (RITUXVAS and EUVAS studies...
concern Vasculitis), and disease in ethnic minorities (ABLE investigates the incidence of kidney disease in the South Asian and African-Caribbean communities). KRUK has co-funded successful studies in partnership with pharmaceutical companies, including a vascular calcification study and a transplant outcome study. There are substantial investigator led and sponsored, but industry funded, trials (particularly in transplantation), which demonstrate the capacity of the renal community to engage with pharmaceutical companies whilst retaining intellectual leadership of the studies.

There are a number of studies investigating the descriptive epidemiology of CKD and its population determinants in a diverse range of populations (e.g. Northern Ireland, Grampian, West Midlands, Kent, West London), many funded by KRUK. Studies of the incidence of CKD in high-risk groups (e.g. obese (Sheffield study), ethnic minorities (ABLE)) and the consequences of CKD in the elderly are ongoing. The UK Renal Registry and UK Transplant provide robust national data to define the epidemiology of RRT and factors influencing prognosis, which can be supplemented by more detailed studies in a selection of units, as has occurred in transplantation, satellite haemodialysis and peritoneal dialysis.

Existing research capacity in the renal community

The UK renal community is a small but integrated community. Since 1950 it has obtained academic leadership from the Renal Association. The infrastructure of the Renal Association has recently been reviewed and reconfigured and it is well placed to support an active and high quality kidney research community. The Clinical Trials Committee of the Renal Association organises and advises on trials in kidney disease. The Research Committee has recently reported on areas of high priority research that are deliverable and have a sound scientific base. There are 73 adult and 13 tertiary referral paediatric kidney units in England, Scotland and Wales and from 2006, all units will input data into the UK Renal Registry which can be interrogated for audit and research purposes and is publishing actively (see http://www.renal.org/Registries/registries.html). The registry is part of the Renal Association but is self-financing and has its own internal management structure. A systematic review of current kidney research and clinical science has been commissioned by the Research Committee of the Renal Association. This will provide an extensive database of all clinical investigators and renal scientists in the UK, as well as their areas of interest.

The Renal Association has developed strong links with other organisations, including related specialist societies such as the British Transplantation Society, British Association for Paediatric Nephrology (BAPN) and British Renal Society, with all of which there have been joint meetings in the recent past. The British Transplantation Society advances the study of the biological and clinical problems of tissue and organ transplantation. While not restricted to kidney transplantation, it maintains strong links with the Renal Association, with many practitioners being members of both organisations. The BAPN is concerned with the care of children with kidney disease. An important aim of BAPN is to conduct multicentre trials and other research that is pertinent to children. The interests of the multidisciplinary team are served by the British Renal Society which has a small but developing research base. Patients are represented both within KRUK and also by the National Kidney Federation (NKF), the federation of local kidney patients associations, run by kidney patients for kidney patients.
Kidney Research UK (KRUK, previously the National Kidney Research Fund) is by far the largest charity in the UK that is dedicated to funding kidney research. It has a well-developed Research Grants Committee, which undertakes peer review and recommends funding of unrestricted Project Grants and Fellowships for clinicians and non-clinical scientists. KRUK also works in partnership with other organisations, e.g. the Medical Research Council, Diabetes UK and the pharmaceutical industry, to jointly fund and coordinate specific projects of importance to the renal community. It supports the Clinical Trials Committee of the Renal Association, and jointly funds a multidisciplinary fellowship with the British Renal Society. It has an extensive database of renal research activity across the UK. KRUK shares the aims of the Renal Association in developing stronger links between all of the organisations involved in kidney research and patient care. This integration and cross-fertilisation across the renal community has allowed it to retain a cohesive approach and to practise 'joined-up thinking' when faced with new challenges.

Historically, the UK renal community has been academically dominated. This should have a positive effect on translational research, as it will allow the long-standing expertise in laboratory-based renal science to support experimental clinical studies, as well as provide the capacity to build in 'added value' to conventional clinical trials, e.g. through pertinent sub-studies and bio-banking. It is, however, important that all members of the renal community have the opportunity to take part in clinical trials in renal disease, which should be provided by a UK Kidney Research Consortium. At present, the capacity for large, multicentre clinical trials is limited by poor national infrastructure and inadequate access to data management and statistical support.
III: Proposal for a UK Kidney Research Consortium

Mandate

The UK Kidney Research Consortium [UK-KRC] will foster the development of UK centres of excellence in a number of kidney research areas. These will include clinical and epidemiological studies, and health services research as well as laboratory science. Collectively, the centres will reach out to include all renal units across the UK. The UK-KRC will aim to provide the best research for best health in relation to kidney disease, but also in relation to the impact that kidney disease has on a range of chronic conditions such as diabetes and cardiovascular disease, including hypertension and stroke. The Consortium will seek added value in fostering the translation of basic science research into the clinical arena. This will also be supported by a growing number of large-scale epidemiological studies to inform and direct the research agenda.

Organisation

Five sub-groups can be developed as part of UK-KRC:

1. Public health and epidemiology of CKD: linking with UKCRN Diabetes and Stroke networks and the Medicines for Children network, as well as with the genomic epidemiology and primary care research networks.

2. Health Services research, i.e. evaluation of NHS service delivery relevant to Chronic Kidney Disease, Established Renal Failure, and Acute Renal Failure and linked to activities of the UK Renal Registry. Given the expansion in provision of care for CKD via primary care, there will be a need for evaluation of ERF service organisation, such as with shared care schemes, co-ordinators, new models for providing vascular risk management, and transition from childhood to adult services.

3. Basic and clinical science research in priority areas such as renal remodelling (a broad research theme investigating cellular and molecular approaches to a range of disease processes, including glomerulonephritis, vasculitis, hereditary renal diseases, and renal fibrosis), diabetic nephropathy (Diabetes network), and cardiovascular complications of CKD (Stroke network).

4. Clinical trials in priority areas, such as halting progression of CKD, that will be developed across all renal units in the UK.

5. UK Renal Genetics Group - developing from the existing UK group, based on the current DNA collections (funded by MRC and KRUK) in renal disease.

UK-KRC could be nurtured under the joint umbrella of the Renal Association and Kidney Research UK, with appropriate input from the Clinical Trials Committee, Research Committee, Registry Committee and Standards Committee of the Renal Association, and from the Research Strategy Committee and Research Grants Committee of KRUK. Other bodies with an integral interest in UK-KRC, such as the British Transplantation Society, British Association for Paediatric Nephrology and the British Renal Society, would be appropriately represented from the outset.
The UK-KRC will be integrated with the National Institute of Health Research initiative. The UK-KRC will foster the development of kidney research within the Biomedical Research Centres that have been proposed in Best Research for Best Health. Further, the UK-KRC would link to the planned Comprehensive NHS Research Network (CRN) and its Comprehensive Local Research Networks (CLRN, which would encompass groups outside of the Biomedical Research Centres), and link to equivalent bodies as the CRN within the devolved administrations of Northern Ireland, Scotland and Wales. UK-KRC would provide input to development of Technology Platforms, Programmes of Applied Research, Primary Care initiatives, and other ventures as appropriate. Close links with KRUK will ensure the identification of strategic research and funding opportunities. Given the extensive but fragmented base for experimental renal medicine and translational kidney research that already exists, linking and networking would have a rapid impact to strengthen and extend its scope.
Aligning specific UK-KRC projects with networks that have already been instigated by UKCRN would allow rapid progress in areas such as diabetes mellitus (a major cause of CKD) and stroke/cardiovascular disease (a major cause of morbidity and mortality in patients with CKD). KRUK has already been in discussion with the National Coordinating Centre for the Diabetes Research Network, and the possibility of collaboration is being considered.

We anticipate funding requirements for key individuals:

1. A National Lead for Kidney Research - likely a clinician with funded PA's to sustain these duties.
2. Project manager - full time. Probably a non-clinician working closely with the National Lead.
3. Kidney research nurse(s) to support each sub-group: i) Public health and epidemiology of CKD, ii) Health services research: ii) Basic and clinical science, iii) Clinical trials, iv) Renal genetics. Clinical data and sample collection are important in all these areas. Experience shows that research nurses provide the most reliable and cost-effective staff group to achieve high standards thereof.
4. Kidney research personnel to support studies in those Biomedical Research Centres with a focus on kidney research.
5. Research Training Lead to provide added value in terms of dissemination of best research practices.

Additional support for specific projects, including kidney research nurses and scientists, would be sought as driven by clinical research priorities.

We also anticipate a need for funding for the following:

1. Meetings to develop multi-centre projects/proposals.
2. Partnerships with clinical trialists.
3. Statistical and data management support.

We anticipate that the UK-KRC will be assessed on the following deliverables:

1. Patient involvement - including numbers entering trials and their geographic distribution
2. Impact on clinical care
3. Publications
4. Grant support from partner organisations, e.g. MRC
5. Investment from industry
References

Appendix

Phase II trials

UKATT: randomised trial of different treatment regimens in low risk and high risk patients with AL amyloid. Aiming to recruit 48 in the UK, starting in 2007. Funding from CRUK.

Phase III trials

MRC trial of membranous nephropathy: randomised trial of immunosuppression for membranous nephropathy with progressive renal dysfunction. Sample size 120 recruited by 2007. Funded by MRC and KUK.

ASTRAL: randomised trial of revascularisation versus medical management only in renovascular disease. Sample size 750 recruited by 2007. (www.astral.bham.ac.uk). Funding from MRC, KUK and PHARMA

SHARP: randomised trial of lipid lowering with simvastatin and exetimibe on the risk of vascular events in chronic kidney disease. 9000 recruited globally by 2006 from 350 hospitals in 18 countries. (www.sharpinfo.org) Funding from PHARMA

EUVAS: European Vasculitis Study group. A sequence of eight randomised clinical trials conducted in the EU since 1995 evaluating therapies in systemic vasculitis. 830 recruited to date. (www.vasculitis.org) Funding from KUK and PHARMA.

MERIT: randomised trial of plasma exchange in myeloma and acute renal failure. Currently recruiting, sample size 286. Funded by the Leukaemia research fund and CRUK.