

**Rare Kidney Diseases:**  
**An Integrated Strategy for Patients in the U.K.**

The Renal Association and British Association for Paediatric Nephrology

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## 1. Executive Summary

In June 2009 the EU Council adopted the final recommendation for European action in the field of rare diseases. This required member states to improve the access of patients with rare diseases to high quality health care. The importance placed on this in the UK is reflected in the 2009 Annual Report of the Chief Medical Officer in the chapter "Rare is Common".

Contemporaneously, the Renal Association and the British Association for Paediatric Nephrology have developed a strategy for patients with rare kidney diseases. It contains our vision for improving standards of care and equality of access, and indicates how we intend to respond to the challenge. A special aspect of the strategy is the integration of clinical care pathways, diagnostic services, disease registers, translational research and audit. Central too is the participation and empowerment of patients at all of these levels.

Implementation of this strategy depends on three key developments

### *a) Development of disease-specific working groups*

Working groups will be established for each disease or group of related diseases. They will develop proposals for seamless integration of diagnostic and treatment services, and patient information. They will undertake audit and research to improve the effectiveness of care pathways. Promotion of the provision of equity for all those with rare diseases, particularly those hitherto underserved, is central to this strategy. The planned governance structure for these groups within the Renal Association is designed to ensure that this evolves.

### *b) Development of care pathways*

These will be disease specific and take into consideration the age of presentation, the nature and range of clinical manifestations, the diagnostic process, the logistics and constituents of treatment, co-morbidities, psychosocial issues and end of life care. They will also address the necessary balance between convenience of care closer to home and the need for highly specialized services that can only be provided in a few centres. Care pathways will be linked to specific, high quality information both for patients and clinicians.

### *c) Development of a UK Registry for Rare Kidney Diseases*

An essential first step to understanding any disease is the collection of informative clinical data. A comprehensive UK Registry for rare kidney diseases (eponym Renal RaDaR) is being developed with MRC and Kidney Research UK funding. It operates within the UK Renal Registry, a highly sophisticated registry for patients with end stage renal failure. Here the existing technical expertise, management and governance structure will help to ensure success. The registry will seek longitudinal funding from capitation in respect of its audit function, and grants for specific projects.

Overall, the strategy offers a systematic and comprehensive approach. It demands a close collaboration between professionals, patients and their supporters. It addresses the needs of children and adults equally, and provides a base from which to resolve the difficult issue of transition of adolescents. It is poised to advance the commissioning of services to patients through a better understanding of rare diseases, response to treatment and the impact on individuals and families. The strategy is novel, open to evaluation, and likely to evolve further. The Renal Associations has the machinery to revise it in the light of experience. Although it is a national strategy it is outward looking, being aware that for many rare diseases sharing of information and expertise internationally is essential.

## **2. Introduction**

A rare disease can be defined as having such a low incidence that it cannot be studied effectively on patients drawn from one, or even a few, medical centres. Most doctors are unlikely to have much experience of it, and will rely heavily on external information in order to offer advice or treatment. The problem is amplified because good quality clinical and scientific information is difficult to capture, and may not exist. Many rare diseases are complex and have genetic or metabolic causes. Treatment is less likely to be developed and tested than in the more common disorders.

Patients with rare diseases often have a sense of isolation. For some the diagnosis is slow to be recognised, and this may reduce confidence in the healthcare system. Standards of care can vary depending on local expertise. Today, patients who have been given a rare diagnosis are likely to scan the internet for scraps of information or contact with other patients. This can be demoralising if the information is misleading, as is sometimes the case. There is a dearth of soundly based literature for specific patient groups, largely because of the scarcity of reliable clinical scientific publications on which to base it. For some of these conditions there are already patient support groups, but for many there are not.

Given that a high proportion of rare kidney diseases have a genetic background, they are often first expressed in childhood. In fact all destructive kidney diseases in childhood are rare. For this reason, clinical services for children with kidney disease are focused into 13 "tertiary" paediatric nephrology centres in the UK. The success of chronic and end-stage renal failure programmes in childhood now permits many severely affected patients to survive into adulthood, which has new clinical and psychosocial implications. Renal teams are caring for young adults with certain rare diseases for the first time in history.

In addition, certain rare diseases manifest for the first time in adulthood, or have only recently been recognized as rare subgroups of more common disorders. Some will have inheritance patterns that imply that other family members are at risk, a group that has largely been overlooked until recently. Generally, few clinicians will have a significant body of experience of recognizing and managing such disorders, which diminishes patient confidence.

The genetics revolution of the last 20 years has profoundly altered the prospects for rare diseases. Many monogenic disorders (diseases caused by a fault in a single gene) have now been described, and more are certain to be discovered. A precise diagnosis may be established by a genetic test, removing uncertainty for patients. Identification of a particular faulty gene has sometimes led to the development of new treatments for that disease, some of which are in clinical trials. Often, the function of the protein encoded by a faulty gene is known or can be predicted, and the scene is set to understand how this leads to a disease. Models of disease can be expressed in cells or animals, and novel concepts of treatment can be put to the test. Moreover, insight into monogenic disorders may allow us a better understanding of normal biological processes as well as of commoner polygenic and acquired diseases.

There is political pressure to capitalise on new technologies to advance the cause of patients with rare diseases. This pressure is necessary. Some of the major drivers of health improvement are not automatically geared to invest in rare diseases. For example, the pharmaceutical industry may not see a return on development costs. Likewise, priorities in health research funding have often been directed towards prevalent common degenerative diseases and cancer. However, patients with rare and complex disorders require lifelong healthcare. Thus, although individual conditions are rare, in total they represent a high cumulative cost to the NHS. The Wanless Report [Crown Copyright 2004; ISBN 0-947819-98-3] recognises that the care of patients with chronic diseases poses the biggest challenge to the future financial stability of the NHS, and that full engagement of such patients with their own care offers the best results, both clinical and financial. Current funding arrangements for treatment are piecemeal and inconsistent. A systematic approach to diagnosis, monitoring and treatment would promote equality of access to health care, and advance both productivity and the quality of care.

The UK Government has adopted the European Union Council recommendation on action in the field of rare diseases, which was accepted by all member states on June 9<sup>th</sup> 2009. The importance of disease registries was highlighted within this recommendation. A national alliance, Rare Disease UK, will maintain the momentum towards implementation of the recommendation by 2011. The Renal Association and British Association for Paediatric Nephrology have both become members of RDUK.

This document indicates the response of the Renal Association and the British Association for Paediatric Nephrology to the present need for better care for patients with rare kidney diseases. It proposes an integrated strategy that will bring together clinical care pathways, diagnostic services, research and audit. It maps onto the evolving national plan for rare diseases. If it is shown to be successful it will have generic utility beyond renal medicine. Central to each level of activity is the participation of patients and their families.

### **3. Integrated models of care**

#### **3.1. Background**

Patterns of disease recognition and care provision for children and adults with rare renal diseases are not identical. Children with these disorders are currently identified by general practitioners and local paediatricians and transferred for advanced diagnosis and treatment to their regional Paediatric Nephrology centre. Each of these "tertiary" centres serves a population of about 1 million children. They are all in main teaching hospitals with other paediatric sub-specialties and diagnostic services such as pathology and radiology, metabolic clinical chemistry and clinical genetics. There are 10 such units in England and one each in Scotland, Wales and Northern Ireland. This centralised system is set to continue, and paediatric nephrologists increasingly cooperate at a national level to improve expert opinion and standardise care pathways.

Because kidney disease is far commoner in adults, there are about seven centres for the treatment of adults with kidney dysfunction for every one regional paediatric renal centre. Some of these are in regional centres with specific areas of research and expertise. Others are in smaller hospitals (formerly called district general hospitals). In addition, the issue of transition and transfer from paediatric to adult care is complex. The Renal Association and the British Association for Paediatric Nephrology have issued joint advice, endorsed by the Royal College of Physicians of London, and accepted by the Department of Health, concerning the professional standards that need to be adopted to safeguard the wellbeing of young people with severe kidney disease who transfer between paediatric and adult care. (Helping adolescents and young adults with end-stage renal failure" British Association for Paediatric Nephrology and the Renal Association 2009). Those standards map directly to this strategy.

There is always a tension between the convenience to patients of providing medical care as near as possible to home, and the needs of those requiring highly specialised services that might only be accessed by travelling long distances. This also creates geographical inequity. However, although only a minority of rare diseases is so complex that day-to-day management needs to be delivered by a specialist centre, for some this is clearly the case - particularly for metabolic diseases where survival into adulthood is novel. Thus for many rare diseases, a combination of periodic specialist review and advice needs to be combined with local support. Paediatric services have to a considerable extent developed such shared-care networks within their region or devolved nation. Parallel networks for adult renal units will be required to offer sufficient flexibility between local and centralised specialist care for rare diseases. The transition and transfer of teenagers and young adults with rare kidney diseases is therefore also dependent on effective regional networks of adult renal centres.

Another factor to be considered is that some of the rare diseases that affect the kidney have extensive clinical expression in other parts of the body and will present to doctors other than nephrologists. For example, within the family of kidney diseases that are caused by defects in the primary cilium (polycystic kidney diseases, juvenile nephronophthisis, Bardet Biedl syndrome, Meckel's syndrome *et*

*cetera*) there are some, for example Bardet Biedl syndrome, in which the renal component appears late. These individuals may therefore be followed by paediatricians and/or endocrinologists for some time before the onset of hypertension and renal impairment directs them towards nephrological care. These are some of the most complicated when it comes to managing their chronic kidney disease.

The growing identification of genetic causes for many of these diseases also mandates closer operational links between nephrologists and clinical geneticists. Genetic services are currently organized at a regional level, with clinical care delivered through peripheral or sub-regional clinics in a ‘hub and spoke’ model. This model may facilitate closer interaction between clinical geneticists and teams involved in the care of rare diseases.

### 3.2. The Chronic Care Model

The ‘Chronic Care Model’ of Wagner and colleagues [Epping-Jordan, J E et al. *Qual Saf Health Care* 2004;13:299-305] describes a systematic approach to optimising the care of patients with chronic disease, and involves the recognition that health-care providers are occasional visitors in their patients’ lives.

There is evidence that disease management programmes that use this model result in better outcomes than would otherwise be the case, at least for some common chronic diseases such as diabetes. While research demonstrating its benefits for rare chronic diseases has yet to be done, there is logic in applying the same principles to these life-long diseases, and reason to expect that the benefits would be even greater than in more common diseases.

The model recognises three levels of care: the individual patient, the community, the healthcare system.

At the level of the **individual patient**, the best outcomes are obtained when well informed patients take an active interest in their own management, in partnership with well-prepared, proactive teams of care-givers.

At the **community level**, resources and policies can support patients with chronic diseases – in some rare chronic kidney diseases this should include, for example, recognition of the impact of the disease on schooling or employment.

At the level of the **healthcare system**, four elements should be considered;

- the design of the **healthcare delivery system**, e.g. regional clinics *versus* outreach specialist clinics;
- **information systems**, e.g. electronic medical records designed to support long-term management;
- **decision support** for clinicians, including reminders for regular screening, ideally integrated into an electronic medical record or, as proposed in this document, supplied by a disease-specific registry (see section 5);
- support for **self-management**, e.g. giving the patient the ability to see their laboratory test results and clinic letters on a website, or to enter their own observations (such as blood pressure; urine specific gravity; weight and height) onto an electronic medical record (see section 9).

Audit tools – specifically designed to assess to what extent the patient feels in control of their own disease and treatment – are currently being developed for patients with diabetes by the ‘year of care’ team within the Department of Health; these tools should be adapted to assess the value added during consultations for patients with rare kidney diseases (see section 8).

### 3.3. Care pathways for patients with rare renal disease

The ideal care pathway for any rare disease needs to take into consideration:

- the age of presentation
- the nature and range of clinical manifestations
- the diagnostic process
- the logistics and constituents of treatment
- co-morbidities

- psychosocial issues
- end of life care.

Developed from these generic headings, each disease-specific pathway will be unique and holistic. The age of presentation determines the route by which patients are diagnosed: some presentations are uniquely paediatric, some uniquely adult, and others occur across the ages. The diagnostic process may demand specific tests – biochemical, histological, and increasingly genetic - that are only available in certain laboratories (see section 4, and Appendix 2). The frequency and complexity of treatment can vary widely, such that while some patients need regular review at a regional centre where expertise is focused, others might only attend such a service on special occasions, for example for a multidisciplinary evaluation or for a single consultation with experts over diagnosis or prognosis. Where appropriate, care should be provided as close to home as possible, and include psychosocial and end of life considerations.

Transition clinics may be needed for the transfer of teenagers from paediatric to adult medical care, either because of the proximity of end-stage kidney failure or because of the complexity of the clinical management of a rare disease and the impact that it has on the normal adaptation to independent living, employment and sexuality. Co-morbidity is a major issue in some disorders, and patients end up seeing several different specialists to diagnose and treat the additional components of their disease. Integrated management can be a challenge and involve disciplines in addition to renal medicine. To give two examples: a patient with cystinosis may require expertise from ophthalmology, neurology and metabolic medicine; a patient with Bardet-Biedl syndrome may require expertise from endocrinology, ophthalmology, hepatology, and audiology .

As disease-specific care pathways become established, there will need to be agreed mechanisms by which they become adopted at a national level, to ensure equitable access and appropriate funding. The geographical centring of service delivery for these new pathways will depend on their rarity and will require a balance between the current location of both clinical and research experts and the demographics of each condition, and must also take into account future training for the next generation of nephrologists.

Provision of care for some of the rarest disorders will require national commissioning. Further training to close knowledge gaps may be required in some instances, so that local nephrologists can participate in shared care.

Care pathways will need to indicate where centres able to offer special or specific tests are located, what investigations/samples are required, and indicate the cost.

### **3.4. Disease-specific working groups**

Each care pathway will need to have specific arrangements for its design, commissioning, audit, and patient empowerment (see sections 7-9). For this to happen there will need to be *rare disease working groups* (RDWGs). RDWGs will ensure a holistic approach to clinical care and champion the cause of patients with a specific disorder. These groups will be professionally led, but must include patients and their representatives and involve them in the process (see Appendix 1). Professional responsibilities should appear in job plans. For some professionals their involvement will reflect a research interest and this is covered in section 6. Others may bring expertise in different areas such as patient education, clinical audit or specialised diagnostic services. The working groups will also be ideally placed to design optimal patient information materials (section 9). They will also engage and advise commissioners. To undertake all these activities the groups will need wide-ranging membership to fulfil their remit.

As a principle, for each disorder or group of related disorders there should be seamless vertical integration of diagnostic and treatment services, audit and research, patient information and empowerment. Disease-specific working groups will need to capture this level of integration and this will influence their manpower and organisation. They are likely to be heavily dependent on the function of the proposed UK renal rare disease registry [acronym: Renal RaDaR - **r**are **d**iseases **r**egistry], outlined

below (section 5), and will therefore be subject to the governance structure of that organisation. A model of good practice for RDWGs is appended to this Strategy. It will be up-dated by Renal RaDaR on behalf of the Renal Association, and will be available on the RaDaR website.

This strategy and Renal RaDaR will also need to encompass the challenge that not all rare kidney diseases fall neatly into a uniform pattern of recognition. Some disease-specific working groups may have a considerable component of researchers or advisers who are not nephrologists. Some non-nephrologists may elect to use the Renal RaDaR platform to further their work. Others may develop care pathways, audit and/or research outside this, but they will need to be cross referenced to the Renal RaDaR website described below. There will need to be continual vigilance to ensure that this renal strategy interfaces seamlessly with parallel initiatives that are certain to be developed by other clinical groups.

#### **4. Diagnosis**

A wide range of investigations may be used in making a diagnosis, including histological, biochemical, dynamic (functional) and genetic testing. Some are available at only limited numbers of centres where special expertise exists, or in the case of genetic tests, at single designated nationally accredited centres. It is important that clinicians know what diagnostic help is available, what tests are appropriate and how they can be accessed. This information is an essential part of a disease specific care pathway. In this strategy we propose to embed this service information in the RaDaR website where it can easily be found, and make RDWGs responsible for the accuracy of the advice.

##### **4.1 Monogenic disorders and genetic testing**

Many rare renal disorders are primarily genetic in origin. Over the past decade there has been a remarkable expansion in identification of specific DNA abnormalities involved in a wide variety of these conditions. This not only has the potential to lead to changes in the management of individual syndromes, but also has major implications for preventative intervention for at-risk family members, whose needs in terms of preventative care have never been systematically addressed. It also, launches new research.

Genetic testing in the UK is commissioned regionally. Accreditation of such tests, through the UK Genetic Testing Network (UKGTN), is an essential prerequisite for their general availability. However, while an increasing number of rare diseases are becoming recognized as heritable, the pace of provision of genetic tests in routine clinical service lags behind. Compared with the number of known inherited disorders involving the kidney, the currently available UKGTN portfolio of approved tests is small. A contemporary list is provided in Appendix 2. These tests have usually been developed following research by individuals with sub-specialty interests in particular disorders. Rigorous quality control is required. The recent development of high-throughput sequencing and SNP array technologies is likely to transform the efficiency and accuracy of genotyping and reduce cost. However at present, most tests require direct sequencing of genomic DNA from patients; others require micro or macro gene or allele deletion screens. For some very rare disorders, international collaboration is needed, as investigation may only be available in other countries.

It is notable that the dissemination and integration both of genetic knowledge and newly determined molecular diagnostic tests into the provision of renal care is not at present matched either by adequate resources or by a structured approach from genetics services to meet demand. Resource for the translation of genetic investigation from research laboratory to service provision afforded by the Biomedical Research Centres is facilitating progress in some geographical areas. However, there is currently no straightforward process that avoids the need to engage a variety of funding streams to underwrite provision of genetic tests, which opens the possibility of commercial genetic testing providers introducing further inequity.

Genetic diagnosis is often important for one or more of the following reasons:

- optimizing therapy
- evaluation of potential donors for living related kidney transplantation
- exclusion from unnecessary follow up when at-risk relatives have negative tests
- patient knowledge, empowerment and concordance
- as a tool to direct pathophysiological investigations and understanding (see 5. Research)
- predictive testing in some conditions

Some single-gene disorders may in due course prove informative about the genetics and pathogenesis of much commoner conditions where there is a prominent renal component, such as diabetes or hypertension. At present, the search for the genetic components of these polygenic complex trait disorders lies well beyond the remit of diagnostic genetic screening. But the single gene disorders within these commoner clinical spectra (for example MODY [maturity onset diabetes of the young] and inherited hypertension such as Liddle syndrome and glucocorticoid remediable hyperaldosteronism) should be sought regardless of whether renal damage has yet been sustained

It is not envisaged that every patient with a phenotypical inherited disorder will require genetic screening. Circumstances where genetic testing is advisable include

- when the disorder is dominant, to confirm the diagnosis and facilitate assessment of at-risk family members
- pre-natally where the disorder or its prognosis may be so severe that the pregnancy would be terminated if the diagnosis were confirmed, or when there is threat to the mother's health by continuing the pregnancy
- when differentiating between similar conditions where management is not identical
- where there is a cancer syndrome

#### **4.2 Non-genetic investigations**

Whether or not genetic investigation is needed, in most cases a combination of specialist clinical observation, biochemical/enzymatic tests, molecular biological, histological and/or whole-patient dynamic tests are required to reach a diagnosis or to monitor metabolic abnormalities and disease progression. Examples of each of these include slit-lamp examination of the eye and quantification of intracellular cystine in cystinosis, quantification of plasma and urinary oxalate in primary hyperoxaluria, ApoE isoform typing in lipoprotein glomerulopathy, and urine acidification testing in distal renal tubular acidosis, respectively. Some of these investigations are complex and/or time-consuming, and are only undertaken in a few laboratories. In only a few rare kidney diseases can the diagnosis be made by kidney biopsy alone.

It will be important for the disease registry proposed below to provide linked information about diagnostic algorithms for individual rare disorders both for care providers and for patients and their families, together with links to the relevant testing provider(s) and centres of excellence. For development of care pathways that are regional, it is possible that clinicians at centres holding UKGTN approval for a particular test will form the hub.

### **5. Proposal for Renal RaDaR - a UK Registry for Rare Kidney Diseases**

#### **5.1 Background**

An essential first step towards understanding and optimizing management of any rare disease is the collection of informative clinical data. Specific disease registries have been assembled from time to time, usually by a small number of enthusiastic clinicians and clinical scientists. Such registries are seldom sustainable as they operate through short term charitable funding, often without administrative infrastructure.

The case is strong for a single, sustainable registry for all rare kidney diseases, within which each specific disease has its own team of professional advisers. A single system would operate to a uniformly high standard of data security and management, overseen by a unitary system of governance and ethics. Such a system would be both efficient and cost effective, and it would serve several needs. These include research and clinical audit, as well as providing a platform for improving clinical care, identifying health economic costs, and engaging patient participation.

## **5.2 Current infrastructure - UK Renal Registry**

The UK has a highly sophisticated and comprehensive national registry for patients with end-stage kidney failure, the UK Renal Registry (UKRR). UKRR operates under the governance of the Renal Association. It is sustainable because it has income based on capitation of all registered patients, and because its audit output is seen as essential to the requirements of the NHS, including collection of the National Renal Dataset, and delivery of the National Service Framework. Registry analyses are also critically important for planning of future provision and for assessment of equity of access and outcomes.

## **5.3 Renal RaDaR: development & content**

Treatment of rare kidney diseases is often particularly expensive and costs need to be properly understood so that services can be planned appropriately. Therefore a UK Registry for rare kidney diseases (Renal RaDaR), operating on the same lines as UKRR, is a main proposal in this strategy. This will be a web based system that will be capable of collecting extensive and detailed ("granular") clinical and laboratory information that can be regularly updated over time to follow the clinical course of a patient. The *rare disease working groups* established under this strategy will take responsibility for developing the relevant web pages in RaDaR. These will include educational material, management algorithms and external links. They will also make proposals for additional data items to be considered for inclusion in the National Renal Dataset.

Patients will be invited to participate in the registry by their nephrologist. They or their parent/guardian will be required to give consent for their clinical details and personal identifiers to be held by the registry. A condition of the generic consent to participate in the registry is that patients can also be approached by researchers in the appropriate working group (see section 6). However, separate research consent will be needed for research projects, which will all require ethics approval.

Patients or their responsible carers will be provided with password access to both their own clinical data and any available disease-specific information. This will operate in the same way as Renal Patient View, a web-based facility in which patients with kidney disease are able to view personal information including laboratory test results, with 'help' fields to explain the meaning of each measurement, and clinic letters. Renal RaDaR will be linked to the UKRR so that consenting patients with rare diseases can continue to be followed automatically after reaching end-stage kidney failure, should that happen.

This model will support best clinical care and facilitate audit, and is designed to be flexible to allow working groups to include those specifically interested in research, patient empowerment or liaison with relevant industry partners.

The Renal RaDaR database will consist of two parts.

Part 1 is the clinical information entered by the patient's nephrologist; the local investigator. This is held by RaDaR on behalf of research participants and is made available to both the patient and local investigator on the one hand, and to the research group in linked anonymised form on the other.

Part 2 data refers to that generated by the disease specific working group for research and held on Renal RaDaR for the purpose of analysis. This is owned by the disease specific working group and will not be released by Renal RaDaR to any other party without permission. A research group can shift data from part 2 to part 1 if it relates to an accredited investigation that may have utility for patient care.

## **6. Research**

The molecular biological era has revolutionised research into rare kidney diseases. This is true not only for monogenic diseases, where a genetic abnormality leads to full expression of disease, but also for mutations that predispose to a disease that is triggered by other factors. Novel mutations may be identified in a very small number of individuals or even in single families. However, subtle genotype and phenotype variations often occur within a disease, and may impact upon the natural course or the response to treatment. Clinical research invariably requires large numbers of patients and carefully defined cohorts in whom the stage of a disease process is known and the effect of extraneous variables can be reduced or controlled. Disease rarity therefore demands a high level of collaboration between clinicians and research institutions if it is to succeed.

Effective translational research requires an integrated team approach, which must include expertise in diagnosis, clinical evaluation, development of biomarkers, laboratory based proof of pathogenesis, evolution of therapeutic hypothesis, trial design and execution. It is unlikely that all components of such a team can be found in a single institution and inter-centre collaboration is the norm. For some studies international collaboration is needed. Only those nations that have well-developed patient data repositories are in a position to participate.

In this strategy, the *rare disease working groups* will be in a powerful position to drive forward a broad-based research agenda for patient benefit. They will utilise Renal RaDaR for the collection of relevant data. They will obtain specific ethics committee approval that will allow them to investigate participants in the registry according to their protocols.

An advantage of linking research to Renal RaDaR is that while research activity is often intermittent, patient contact will be preserved and new research proposals can be designed in the light of known characteristics of the available patients. This is an aspect specific to work on rare diseases that distinguishes it from the more familiar approach in common disorders. Grant applications by researchers are more likely to succeed where cohorts of patients are well described and their availability known.

## **7. Governance**

Governance of Renal RaDaR will be modelled on the successful structural relationship between the Renal Association, UKRR and Renal Patient View. A Rare Renal Diseases Committee will be established, which will be responsible for all operational aspects of the rare disease registry; it will report to the Renal Association Executive Committee. The Rare Renal Disease Committee will include representatives of the Renal Association's UKRR Committee, members of the UK Kidney Research Consortium, and a representative from the RenalPatientView committee. The chair of the Renal RaDaR Committee will be appointed by the Renal Association. Rare disease working groups will issue progress reports to the Renal RaDaR Committee at specified intervals. These will be the same as for standard research governance and ethics committee reportage so as to minimise bureaucracy.

The contract between rare disease working groups and Renal RaDaR will be based on a *Standard Operating Procedure*. This will clarify who owns, accesses, analyses and reports on the clinical and research information held in RaDaR. The Standard Operating Procedure will set out the expected rules by which the disease specific working group can approach patients. In brief, patients will be recruited and consented via their local investigator and all connection between the patient and the researchers will be link-anonymised. There will be rules governing exceptional action to be taken where results from research investigation, or preliminary data from a trial has an immediate impact on the clinical care of an individual.

There will be firm agreements as to what happens to Part 2 data in RaDaR if a rare disease working group disbands or is absorbed by another research body. If a research group for whatever reason ceases

to conduct active research, but there is an intention that this will resume at a future date, Part 1 data may continue to be collected. Part 2 information will be frozen but reactivated on resumption of research activity.

The organisational structure is shown in Appendix 3. Within the Renal Association the structure for governance of the disease specific working groups will evolve according to experience, and as required to advance the vision of the strategy.

## **8. Audit**

Once established, Renal RaDaR will make annual reports in a similar way to UKRR. Given the high costs of care of many rare kidney diseases, there is a particular obligation to record and publish patterns of uptake for treatment, and outcome data. The disease-specific care pathways, [see Section 2] will be audited against standards, and the pathways adjusted to improve patient benefit. A disease specific example of audit would address the use and value of a monitoring tool, such as leukocyte cystine measurements in the therapy of cystinosis. The latter requires the capture of very detailed clinical information for which the RaDaR system has been designed. The working groups, which will include patient and carer representation, will be well placed to propose topical and relevant audit questions to Renal RaDaR.

## **9. Empowering patients and families**

The major rationale for developing Renal RaDaR is to benefit care of and outcomes for patients. We believe that empowering patients and their families is an important feature of this strategy. The means to achieve this include

- inviting patients or their parents/guardians to participate in all aspects of Renal RaDaR's development, for example there will be patient representation within the disease-specific working groups
- patient representation in the governance of the registry
- confidential access for patients/parents/guardians to their own patient data within RaDaR using password protected access to limited data fields in a read-only mode, as described in section 4
- provision of web links to patient support groups where these exist, and facilitation of the development of new groups
- provision of notices about research and audit activity and links to relevant news feeds
- development of suitable educational material
- inclusion of fields into which patients can enter specified data
- the ability to respond to [for example] quality of life questionnaires and psychological surveys as developed by the disease-specific working group.
- obtaining input from patient representatives to research ethics applications

## **10. Costs and Efficiencies**

The primary goal of improving care for patients with rare renal disease is expected to produce cost benefits. Minimising unnecessary clinic attendance, coordinating visits in multidisciplinary clinics, ensuring that complex high cost testing is used appropriately, reducing complications and hospitalisation are just examples of expected cost reduction.

There are costs associated with the RaDaR initiative which can be viewed as a mixture of fixed and variable.

*Fixed costs* are those needed for the day to day operation of the website and database, including staffing. These costs are only indirectly connected to activity, although it is anticipated that there will be a steady

growth in the early years as more diagnostic groups are included in the programme, and as audit cycles repeat. Fixed costs need a steady, adequate and dependable income stream. It is proposed that after an initial development period this is obtained by capitation, justified as for UKRR: the audit function for the rare diseases being an obligation on the NHS. This cannot be achieved at a more local level, either regionally or within Trusts. The argument for capitation funding is supported on twin agendas of audit and patient empowerment. This frees research income to deal solely with projects that disease-specific working groups propose.

*Variable costs* are those that support individual tasks such as:

- commissioning a new disease-specific data collection;
- cohort analysis to facilitate translational research and clinical trials;
- long term outcome studies.

These activities will be funded by specific research project grants.

However, many awarding bodies do not cover administrative support costs, and are unlikely to fund registry maintenance costs outside specific research projects even though clinical data collection is continuing; hence the need for staff within fixed costs.

Audit of care pathways is also likely to be a disease-specific, variable activity and may be funded by the health service, industry or patient groups. Growing international collaboration on rare diseases is anticipated to generate further activity, in which UK data are added to that in other countries to increase analytical power. This too will involve variable costs, likely to be met from international grants.

The initial establishment of a pediatric rare kidney disease registry has been realised by grants from the MRC and Kidney Research UK awarded in 2009. These grants have allowed for the piloting of two rare disease cohorts: membranoproliferative glomerulonephritis and steroid resistant nephrotic syndrome. Each now has its own disease-specific working group. While there may need to be a transition phase in which new disease-specific working groups contribute to fixed costs, the intention is to separate fixed and variable costs as soon as possible, thus ensuring sustainability of Renal RaDaR.

This financial model is attractive because of its scale and efficiency. Hitherto, disease registries and cohorts each had to develop their own data collection methods from scratch. In this strategy, the set up costs for each additional rare disease will fall as the experience and capability of the registry grows. Many systems will have common application across different disease groups. This will reduce the cost of individual research projects. Less research money will be used in administration, leaving more for analysis. Research grants will be better targeted to the specific task, with less risk of a drift of expenditure to maintain components of the overall registry.

## **11. Summary**

A strategy is proposed to improve the care of patients with rare kidney diseases in the UK. It addresses issues of equality of access to services, care pathway design, improving productivity and quality of care, empowerment of patients and their carers, audit and research. It offers a system to provide expert advice to commissioners.

The strategy applies to all children and adults with rare kidney diseases, and is consistent with the recent recommendations for transition and transfer from paediatric to adult care from the Renal Association and the British Association for Paediatric Nephrology, endorsed by the Royal College of Physicians of London. Although designed for kidney patients it has the potential for generic utility beyond adult and paediatric nephrology.

*Rare disease working groups* will be established for each disease or group of diseases. These groups will develop proposals for the seamless integration of diagnostic and treatment services, audit and research, patient information and empowerment.

*Care pathways* will be developed, which recognise

- the tension between the convenience of treatment near home, and the need to access highly specialised services, which might mean travelling long distances. For many rare diseases, a combination of periodic specialist review and advice needs to be combined with local care.
- the multiorgan involvement of some rare diseases requiring interaction with other specialists
- the growing identification of genetic causes for many rare diseases requiring closer interaction with clinical geneticists, and diagnostic laboratory services in genetics

The pathways will take into consideration

- the age of presentation
- the nature and range of clinical manifestations
- the diagnostic process
- the logistics and constituents of treatment
- co-morbidities
- psychosocial issues

*Renal RaDaR [rare diseases registry]*

Integral to the success of this strategy is the establishment of a single, sustainable UK registry for rare kidney diseases [Renal RaDaR].

- It will facilitate clinical care, audit and research.
- It will be organised within the structures of the UK Renal Registry,
- Disease-specific working groups will develop specific elements in RaDaR building cost effectively on a generic platform.
- Initial establishment of the generic RaDaR platform with short life research funding will be followed by a sustainable funding model based on capitation as presently in place for the UK Renal Registry and Renal Patient View.

Governance of RaDaR will be the responsibility of the Renal Association.

## **12. Appendices**

### **Appendix 1. Rare Kidney Diseases: Good Practice for Rare Disease Working Groups [RDWGs]**

#### **Purpose**

The purpose of RDWGs is to promote and to integrate the following.

- development of evidence based clinical care pathways,
- empowerment of patients with high quality information
- advice to commissioners
- audit of outcomes.
- collaborative translational research for patient benefit.

The following good practice guidance is given in order to achieve this purpose.

#### **Terms of reference**

1. RDWGs should develop "bottom-up" according to professional enthusiasm and clinical need.
2. RDWGs should be made up of clinicians, both medical and allied to medicine, scientists, patients or their representatives, and should have a secretariat.
3. RDWGs should be inclusive and actively seek out partnerships. There can only be one RDWG per disease in the United Kingdom.
4. At an early stage each working group should agree
  - the different roles of its members,
  - the duration of each persons' membership,
  - how it will seek financial support,
  - rules concerning data sharing and authorship of publications.
5. Membership of a RDWG should be in the public domain, and members' names should appear on the RaDaR web site.

#### **Activity**

6. RDWGs are responsible for designing the disease-specific data collection pages for RaDaR. They will expect to meet the set up costs for this disease-specific data collection.
7. The RaDaR database consists of two parts. Part 1 will contain clinical information entered by the local investigator and/or the patients themselves. The RDWG will have access to this information but without the personal identity of the patients. Part 2 of the database is reserved for the RDWG and will be populated with their research information. These data cannot be accessed by the local investigator or the patient.
8. RDWGs should not provide professional advice directly to individual patients.
9. RDWGs should be responsible for identifying or producing high-quality patient information and making it available to patients for example through the RaDaR web site.

#### **Research**

10. Research activity should be an integral but not exclusive activity of the group.
11. All contact with patients for research purposes will be linked-anonymised.

**Governance**

12. In order to use Renal RaDaR, each RDWG will need to sign a Standard Operating Procedure [SOP] agreement. Separate SOPs will be required for individual research projects.

13. RDWGs should hold regular meetings, either face-to-face or virtual, and keep a record of their proceedings.

14. All proceedings should be public as far as possible, with a resume of the minutes to be published on the RaDaR web site where it can be accessed by patients with that disease.

15. RDWGs should have an internal strategy to resolve any conflict of interest or disagreement between members. For professional issues, and those that cannot be resolved internally, external adjudication will be available through the Renal Association.

## **Appendix 2. Applicable rare diseases and UK diagnostic tests [current at December 2009]**

Comments, right hand column:

- 1 Additional genes, unknown
- 2 Active UK research
- 3 Pathognomonic non-genetic (clinical or biochemical) tests available

Shown in **bold** are tests approved by Gene Dossier [the UK Genetic Testing Network (UKGTN)-approved format for request and provision of a genetic test]

<b>Disorder</b>	<b>Gene</b>	<b>Lab</b>	<b>Comments</b>
Alport Syndrome, X-Linked	<i><b>COL4A5</b></i> <i>COL4A4</i> <i>COL4A3</i>	<b>Guys</b>	
Arthrogyrosis, Renal Dysfunction, and Cholestasis	<i><b>VPS33B</b></i>	<b>Birmingham</b>	2
Autoimmune Polyendocrinopathy Syndrome, Type I	<i><b>AIRE</b></i>	<b>Exeter</b>	2
Bardet Biedl syndrome	<i>BBS1-9</i>		2
Branchio-oto-renal Dysplasia	<i><b>EYAI</b></i>	<b>GOS</b>	2
Calcium-sensing disorders (Hypocalciuric Hypercalcemia, Familial, Type I; Hypoparathyroidism, Familial Isolated; Hyperparathyroidism, Neonatal Severe Primary)	<i><b>CASR</b></i>	<b>Oxford</b>	2
Cystinosis, Late-Onset Juvenile or Adolescent Nephropathic Type	<i><b>CTNS1</b></i>	<b>GOS</b>	2
Cystinosis, Nephropathic	<i><b>CTNS1</b></i>	<b>GOS</b>	2, 3
Dent disease	<i><b>CLCN5</b></i>	<b>Oxford</b>	2
Fabry Disease	<i><b>GLA</b></i>	<b>Belfast</b> <b>GOS</b>	2, 3
Gitelman Syndrome	<i><b>SLC12A3</b></i>	<b>Cambridge</b>	2, 3
Glucocorticoid-Remediable Aldosteronism	<i><b>CYP11B1/2</b></i>	<b>Aberdeen</b> <b>Cambridge</b>	2, 3
Goodpasture syndrome			2, 3
Haemolytic-Uremic Syndrome	<i><b>CFH</b></i> <i><b>ADAMTS13</b></i>	<b>Newcastle</b> <b>UCL</b>	1, 2, 3
Hyperoxaluria, Primary, Types I and II	<i><b>AGXT</b></i> <i><b>GRHPR</b></i>	<b>UCL</b>	2, 3
Hyperparathyroidism 2 (with jaw tumour)	<i><b>HRPT2</b></i>	<b>Oxford</b>	2
Hyperuricaemic Nephropathy, Familial Juvenile	<i><b>UMOD</b></i>	<b>Cambridge</b>	1, 2, 3

Hypoparathyroidism, Sensorineural Deafness, and Renal Dysplasia (Barakat syndrome)	<b><i>GATA3</i></b>	<b>Oxford</b>	
Hypophosphatemic Rickets +/- hypercalciuria	<b><i>FGF23</i></b>	<b>Exeter</b>	1, 2
Liddle Syndrome	<b><i>DMP1</i> <i>SLC34A3</i> <i>SCNN1B</i>, <i>SCNN1G</i></b>	<b>Cambridge</b>	2, 3
Lipoprotein Glomerulopathy	<b><i>APOE</i></b>	<b>Sheffield</b>	3
Lowe Oculocerebrorenal Syndrome	<b><i>OCRL1</i></b>	<b>Manchester</b>	2, 3
Maturity-Onset Diabetes of the Young, Type V / atypical FJHN	<b><i>HNF1β</i></b>	<b>Exeter</b>	2
Medullary Cystic Kidney Disease 2	<b><i>UMOD</i></b>	<b>Cambridge</b>	1, 2
Membranoproliferative GN / Dense deposit disease			2, 3
Mitochondrial cytopathies	<b><i>Mitochondrial</i></b>	<b>Oxford, Inst Neurology Sheffield Liverpool</b>	2?
Nail-Patella Syndrome (Fong disease)	<b><i>LMX1B</i></b>		2?
Nephrogenic diabetes insipidus	<b><i>AVPR2</i> <i>AQP2</i></b>		
Nephronophthisis	<b><i>NPHP1</i></b>	<b>Glasgow GOS</b>	1, 2
Nephrotic Syndrome, Steroid-Resistant	<b><i>NPHP2-9</i> <i>NPHS2</i></b>	<b>GOS Manchester</b>	1, 2
Orofacial digital syndrome	<b><i>ACTN4</i> <i>CXORF5</i></b>		
Polycystic Kidneys, Autosomal Dominant	<b><i>PKD1</i></b>	<b>Sheffield</b>	2, 3
Polycystic Kidneys, Autosomal Dominant	<b><i>PKD2</i></b>	<b>Cambridge Sheffield</b>	2, 3
Polycystic Kidneys, Autosomal Recessive	<b><i>PKHD1</i></b>	<b>Leeds Cardiff</b>	2?
Renal Cell Carcinoma, Papillary 2	<b><i>MET</i></b>	<b>Birmingham</b>	2?
Renal Tubular Acidosis	<b><i>SLC4A1</i> <i>ATP6V0A4</i> <i>ATP6V1B1</i></b>	<b>Cambridge</b>	1, 2, 3
Tuberous Sclerosis	<b><i>TSC1</i>, <i>TSC2</i></b>	<b>Cambridge Cardiff</b>	
Wilms Tumour, Denys-Drash/Frasier Syndromes etc	<b><i>WT1</i></b>	<b>St Georges Sheffield</b>	2

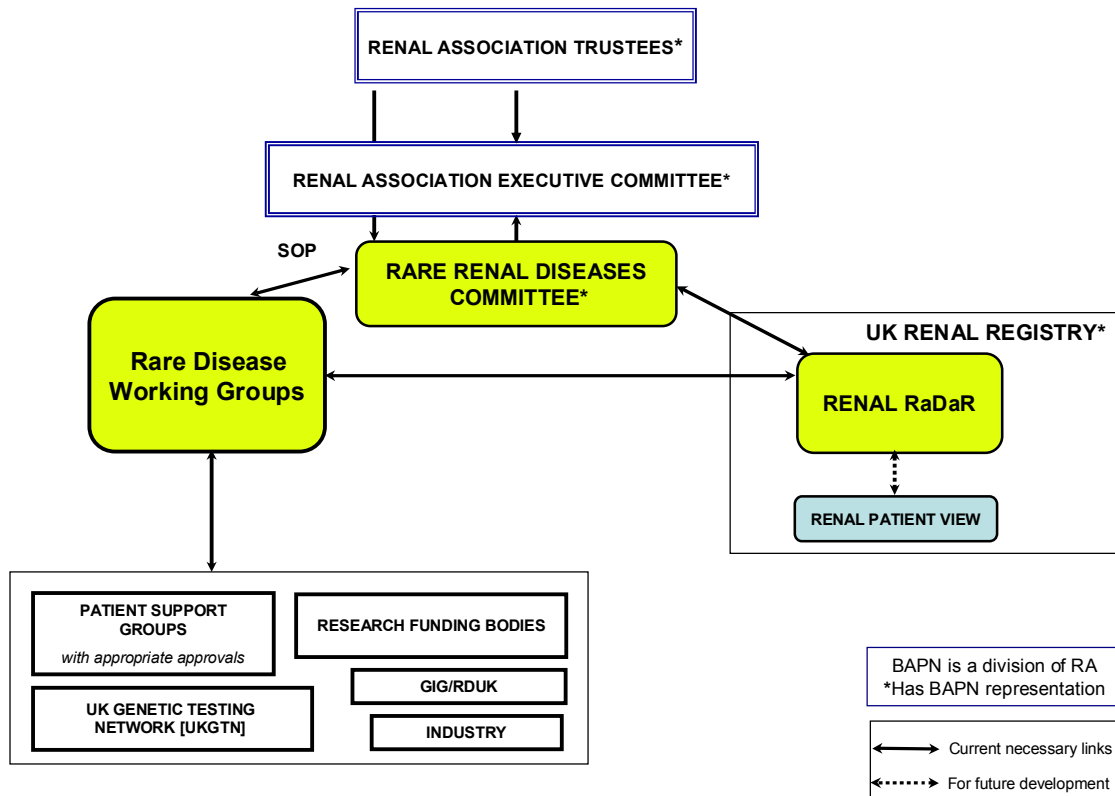
Von Hippel-Lindau Syndrome

*VHL*

**Birmingham**  
**Leeds**  
**Oxford**

2, 3

**Appendix 3 - Organisational chart**



Notes

Renal RaDaR and RenalPatientView have separate, but parallel, governance arrangements within the UK Renal Registry.  
 There will be developing links between Renal RaDaR and Renal Patient View, since RenalPatientView will be one approach by which information for patients and carers developed by disease-specific working groups , will be disseminated.

GIG – Genetic Interest Group – a UK alliance of patient organisations with a membership of over 130 charities which support children, families and individuals affected by genetic disorders

RDUK – Rare Diseases UK, a UK alliance of researchers, clinicians, the pharmaceutical industry, commissioners and government established in response to unmet health care needs of those with rare diseases who need improved access to integrated care and support from the NHS.

SOP – standard operating procedure

#### **Appendix 4. Contributors to the strategy and acknowledgements**

This strategy was prepared by a working group convened by the Renal Association and the British Association for Paediatric Nephrology

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The strategy was prepared by a writing group authorised by the working group – John Feehally, Fiona Karet, Moin Saleem, Mark Taylor, Charlie Tomson, with contribution from Mary McGraw.

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