National Registry of Rare Kidney Diseases. (RaDaR)

Protocol

Purpose

The purpose of the National Registry of Rare Kidney Diseases (RaDaR; rare disease registry) is to facilitate translational and epidemiological research into rare kidney diseases by setting up and maintaining comprehensive clinical databases in partnership with disease-specific research groups.

RaDaR will facilitate the identification of well-characterized cohorts of patients who will be invited to participate in clinical trials, development of biomarkers, phenotype-genotype correlations, or outcome studies. It will inform the development of clinical guidelines for specific rare diseases and it will audit treatment and outcome.

RaDaR will feed back relevant information to registered patients, and allow patients to provide information including their own reported quality of life and outcome measures.

Background

Rare diseases are arbitrarily defined as having an incidence such that they cannot be studied effectively on patient groups drawn from one or a few medical centres.

A high proportion of such disorders have a genetic background and often these diseases are first expressed in childhood. The success of chronic and end-stage renal failure programmes in childhood permit some of these patients to survive into adulthood. There are 13 centres for paediatric nephrology in the UK. For a rare disorder that a paediatric nephrologist might diagnosis only once a year, and assuming 100% survival to adulthood, a renal physician might be asked to take over such a case only once in seven or eight years of practice. Research is hampered by this dilution of clinical experience. Similarly in adult practice there are rare complications of diseases or their treatment so that a nephrologist might encounter such an event less often than once in every 5 years. National aggregation of clinical experience is essential to further study.

Research groups investigating a rare disease (Disease-Specific Research Groups, DSRGs) have difficulty accessing patients who are widely distributed. Our proposal specifically addresses the difficulty in obtaining consent to approach potential participants for their consent to participate in clinical studies. While disease specific research groups are often successful in identifying novel genotypes in a few individuals, it is more difficult to define phenotype, and undertake phenotype-genotype correlations. Moreover, the scarcity of patients makes it difficult to develop biomarkers, or identify well-defined cohorts in which to test novel treatments. As a result, the progression and outcome for many rare diseases are unknown, and treatment remains undeveloped.

The Registry

RaDaR will provide an infrastructure to capture both generic and disease-specific clinical information and to collate longitudinal information. It is designed to increase engagement of patients with these disorders by providing both disease- and patient-specific information, and allowing patients to input their own data.
The registry was set up following an initiative of the Medical Research Council (2008) to develop cohorts of well-categorized patients for translational research. RaDaR is a development of the Renal Association, and is operated by the UK Renal Registry (UKRR). The governance structure is described below.

The registry will be Web-based and data will be encoded and held on a secure server. Data entry will be made by the clinician with responsibility for the patient; usually their nephrologist or paediatric nephrologist. Patients who have consented to participate in the registry will have their own user name and password that allows them to see their own data file, to enter data fields themselves, and to receive information about their clinical condition. Parents and guardians of children who participate in the registry will have similar access until such time as the patient is mature enough to consent for himself or herself, and the right of access is transferred from parent or guardian to the patient. Patients will be given a secure login and password, and be able to view their own data on the Renal Patient View (RPV) website, an existing patient information system, governed by the Renal Association, designed for patient access and information about their renal disease. Consent forms and patient information sheets will include details of how to gain access to this portal.

Data from the registry will be made available to researchers investigating specific rare diseases in accordance with the operating policy enforced by the RaDaR Committee and UKRR (see below).

**Governance**

Governance will be undertaken under the authority of the Renal Association of Great Britain, the professional body for nephrologists in the UK, via its Clinical Affairs Board.

The business aspects and strategic direction of UKRR are overseen by the UKRR Management Board, comprising the Trustees of the Renal Association together with the Director and General Manager of the UKRR. The Management Board is chaired by the immediate past President of the Renal Association. The UKRR Management Board meets face to face annually. Additional virtual meetings of the Management Board are held as deemed necessary by the Chair throughout the year by phone conference or email.

The day to day work of UKRR is prioritised by the UKRR Committee, which reports to the Clinical Affairs Board of the Renal Association. The Chair of the UKRR Committee is appointed by the Trustees of the Renal Association (http://www.renal.org/pages/pages/the-association/memorandum-articles-rules/rules-of-the-association.php).

The National Registry of the Rare Renal Disease is managed by The Rare Disease Committee (RDC) of the Renal Association. It consists of a Chairperson (3yr appointment) and includes representation from the Renal Association, This follows from the Renal Association's "Strategy for Patients with Rare Kidney Diseases" published in 2010. The RDC came into being in December 2010 on the appointment of its chairman Dr C Mark Taylor (term of office 3 years). The rules of the Committee were approved by the Renal Association Executive in February 2011. The RDC has representation from the UK Renal Registry and the Research Committee of the Renal Association, and it reports to the Executive of the Renal Association through Clinical Affairs Board. A working party of the RDC, led by Prof Moin Saleem (term of office 3 years) with input from the systems manager of UKRR undertake the day to day operational management of the database.
The Rare Disease Committee will meet at least twice yearly, a minimum of one meeting being a face-to-face meeting. In addition, committee business will be maintained using e-mail and telephone conferences between meetings. The Chair will prepare written reports of the business of the Committee for UKRR and the Research Committee of the Renal Association, or delegate this task to a secretary chosen from among the Committee membership. The chair will be responsible for keeping the membership of the Renal Association informed of the registry’s activity, and keeping the committee’s website area up to date with information about the current committee membership, minutes of committee meetings, research activity, patient recruitment opportunities and other relevant information. Members of the Committee will usually serve for no more than one term of three years. Members of the Committee will be expected to attend at least one Committee meeting annually and will contribute actively to the work of the Committee as required by the Chair.

Research access.

Researchers proposing to use RaDaR to investigate a specific rare disease will be required to form a Rare Disease Group (RDG). The Rare Disease Committee (RDC) of the Renal Association in partnership with grant awarding bodies such as Kidney Research UK (KRUK) will adjudicate applications. To be successful, a RDG will need to demonstrate compliance with the "Good practice" guideline of the Renal Association Strategy for Rare Kidney Disease (2010) and sign a Standard Operating Procedure with the RDC. The RDG will design the disease-specific data fields for the research information required. Generic data fields are the responsibility of Rare Disease Committee, and will be designed and modified where necessary. The RDG will require separate research ethical committee approval in order to contact patients entered into the registry or to involve them in any research studies.

Ethics

The patient, or in the case of a minor their parents or guardians, will be informed about the registry by the nephrologist or a member of the team responsible for the patient’s care with the relevant patient information sheet being provided in person or by post. Written permission will be sought to be contacted by a member of the research team. Information will be offered in the patient’s first language, either using translation services provided locally within the NHS, or pre-prepared in the case of major languages such as Welsh. Information for children will also be provided. Written consent will be obtained by the patient’s nephrologist or a member of the research team. A copy of it will be held in the patient’s hospital medical record, and a copy sent to the patient’s general practitioner. The referring nephrologist will be required to confirm that consent has been obtained when first notifying the case to the registry. Failure to do so will prevent data from being entered.

For childhood patients, the period of consent will be capped at 18 years, and at 16 years of age an automatic reminder will be issued to the nephrologist that consent will need to be given independently by the patient. This is designed to give adequate time for the research subject to formulate an independent opinion about their participation as adults. Teenage patients can electively consent for themselves before 18 years of age if they wish. If a research subject reaches 18 years of age and has neither consented for himself/herself nor withdrawn, the registry record will be frozen, and the nephrologist and the DSRG will be informed. Patients may withdraw from the registry at any time by notifying the registry in writing. If they do so their data will be removed, and thus any contact with the DSRG prevented. They will be notified in writing that this has been done according to their instruction; their user name and password will be withdrawn. They will
therefore lose their access rights to information about their own data or to disease specific information. The DSRG will be notified of the withdrawal.

RaDaR has received ethical approval from the North Somerset and South Bristol Research Ethics Committee, reference number 09/H0106/72.

**Patient information**

The registry will capture both generic and disease specific information. The former will include patient identifiers. This is justified by the intention of the registry which is to put patients in touch with research opportunities as they arise. Patient information will only be released to a RDG under the terms of the agreement between the NRRKD and a RDG, and with appropriate ethical agreement in place concerning the specific proposal that a RDG will make towards the patient. Generic information will include estimated kidney function obtained longitudinally, the date of end-stage renal failure, the modality of renal failure management and death.

The data fields that are specific for a given disease will be designed by the RDG. The registry will be capable of handling data generated after contact between the patient and the RDG. For example, if a RDG proposed expert pathological review of renal biopsies or genetic analyses that are central to the development of a cohort, and have obtained separate consent to obtain the same, the results of this would be added to patient data held in the registry. This data will be accessible by the patient.

**Funding**

The set-up costs and the first 3 years of operation are provided by grants from the MRC and KRUK (available end 2008). The MRC grant will fund cohort development of two diseases, nephrotic syndrome with focal segmental glomerulosclerosis, and mesangiocapillary glomerulonephritis. In effect this permits the setting up not only of the generic registry but also the first two DSRGs. These two examples will be used to develop and test the system that will be rolled out to additional specific kidney diseases. It is expected that up to 10 specific diseases will be operative within the first 5 years, each of which will bring additional research revenue. However the long-term aim is to maintain funding so that data acquisition can continue during periods when projects become inactive and project funding lapses. For the future, the favoured option will be to apply a capitation fee in the same way as does UKRR. We expect this model of a rare disease registry to be an exemplar for the understanding of all rare disease within the NHS. We propose that the structure will become integrated with the Map of Medicine and Connecting for Health, and will be supported by the National Clinical Audit Advisory Group and the National Institute of Health Research.

The annual budget will meet the cost of staff required to support and maintain RaDaR as well as other maintenance, infrastructure, implementation and development costs. Staff employed for RaDaR will work in the UKRR offices in Bristol, under the same HR arrangements as UKRR staff. If RaDaR employs UKRR staff on a part-time basis, appropriate arrangements for cross cover and necessary training will be agreed between the RaDaR Committee Chair and the management team of the UKRR.