PROTOCOL

FULL TITLE
National Registry of Rare Kidney Diseases

ACRONYM
RaDaR - (*rare disease registry*)

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KEY CONTACT
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1. BACKGROUND

Rare Diseases

Rare diseases are generally defined as affecting fewer than 200 000 individuals in the USA[1] or fewer than five per 10 000 individuals in Europe.[2] Rare diseases cannot be studied effectively on patient groups drawn from one or even several medical centres. Research groups investigating a rare disease have difficulty accessing patients who are widely distributed. While rare disease 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 underdeveloped.

Rare Kidney Disease

Chronic kidney disease is a major global health challenge that can progress to kidney failure. For every 100,000 individuals in the UK, 60-80 will be living with one of more than 150 identified rare kidney conditions. These people account for more than 25% of patients receiving kidney replacement therapy. Despite representing less than 10% of the chronic kidney disease population, people with rare diseases are 28 times more likely to face kidney failure than those in the general population with common causes of chronic kidney disease, such as diabetes and hypertension. They are however less likely to die before needing dialysis or a kidney transplant.[3] The natural histories of most rare kidney diseases are poorly characterised, and the reasons that individuals with rare kidney diseases are over-represented in the kidney failure population are not well understood.

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. For a rare disorder that a paediatric nephrologist might diagnose 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 a nephrologist might encounter a rare complication of a disease or treatment less than once in every 5 years. National aggregation of clinical experience is essential to further study.

Rare Kidney Diseases: An Integrated Strategy for Patients in the UK.

Priorities in health research funding have often been directed towards 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 cost to the NHS. The NHS 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 patients with their own care offers the best results.

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 was reflected in the 2009 Annual Report of the Chief Medical Officer in the chapter "Rare is Common".[4] Contemporaneously, in 2010 the Renal Association and the British Association for Paediatric Nephrology developed a strategy for patients with rare kidney diseases setting out a vision for improving standards of care and equality of access, driving the development of rare disease research in the UK.

An essential first step towards understanding and optimising the management of any rare disease is the collection of informative clinical data. Implementation of the strategy therefore depended first on key developments, including the development of a UK Registry for rare kidney diseases to bring data together and create an essential resource for healthcare professionals and researchers. Additional aspects of the strategy included the integration of clinical care pathways, diagnostic services, disease registers, translational research and audit. Central too was the participation and empowerment of patients at all these levels.

Overall, the strategy offered a systematic and comprehensive approach demanding close collaboration between professionals, patients, and their supporters.

The National Registry of Rare Kidney Diseases

Since the inception of the National Registry of Rare Kidney Diseases (RaDaR; *rare disease registry*) more than 34,000 patients have joined the RaDaR community (figure correct 2024) and the database currently represents the largest collection of rare kidney disease patients in the world. RaDaR considers children and adults to be equally important and provides a base from which to resolve the difficult issue of transition of adolescents to adults.

Examples of successes include:

- Publishing clinical guidance/making clinical recommendations.
- Informing Specialised Commissioning (the process by which health and care services are planned, purchased, and monitored).
- Writing national letters to improve patient care.
- Establishing disease specific hubs and specialised centres.
- Improving coordination of Multi-Professional Team care.
- Identifying people suitable for clinical trials and informing potential participants.
- Introducing novel and improved therapies.
- Identifying disease biomarkers and genetic profiles.
- Driving change in biological sampling techniques.
- Engaging with international and/or global research communities.
- Leading and/or participating in UK and International trials and studies.

2. MAIN AIMS

RaDaR aims to:

1. Facilitate translational and epidemiological research into rare kidney diseases by setting up and maintaining a comprehensive clinical database.
2. Provide infrastructure for individual rare disease studies and sub registries in partnership with Rare Disease Groups.
3. Facilitate the identification of well-characterised cohorts of patients who may be invited to participate in clinical trials, biomarker development projects, phenotype-genotype correlation studies, outcome studies, patient reported experience/outcome studies and other types of research.
4. Better understand the natural history of rare kidney diseases.

5. Audit and research treatments and their outcomes to better understand rare diseases, responses to treatment, long term effects of therapies and the impact on individuals and families.
6. Advance the commissioning of services to patients through quality and service evaluation.
7. Support NHS England in the evaluation of high-cost drugs.
8. Inform the development of clinical guidelines for specific rare kidney diseases.
9. Further the development of future therapies by ensuring high quality data is available to support clinical trials.
10. Improve the quality and quantity of paediatric data that is available for research.
11. Identify areas where new treatments are needed.
12. Facilitate the development of care pathways.
13. Facilitate the integration of diagnostic and treatment services and patient information.
14. Promote the provision of equitable care and empower patients to have a voice.
15. Drive the integration of genomics into general healthcare for rare kidney diseases.

3. GOVERNANCE

RaDaR is managed by the UK Kidney Association (UKKA). The UKKA has a strong bedrock of governance with a Trustee Board, Executive Council, advisory Patient Council and links to key UK Stakeholder Kidney Charities. https://ukkidney.org/governance

The UKKA is supported by an executive, including a Chief Executive Officer (CEO), Marketing and Communications, Human Resources and in-house Secretariat underpinning UKKA corporate delivery. An Operational Leadership Group ensures day-to-day running and delivery of its strategic aims.

The business aspects and strategic direction of RaDaR are overseen by the Rare Disease Committee (RDC), which is chaired by the Academic Vice Presidents (AVPs) of the UK Kidney Association and reports to the UKKA Operational Leadership Group. In addition to the UKKA AVPs, Rare Disease Committee members include all Rare Disease Group Leads, the Director(s) of RaDaR, key members of the senior management of the UKKA, senior members of kidney disease charities and professional associations, and patient representatives.

Operational management is overseen by the RaDaR Operational Management Group (OMG), which translates strategic directives from the Rare Disease Committee into operational activities to be carried out by the RaDaR team. It reports to the Rare Disease Committee.

Requests for analyses of RaDaR data for research projects are reviewed by the RaDaR Data Analysis Group, which consists of the RaDaR Directors, senior statistical, epidemiological and technical members of the UKKA, Finance and Information Governance specialists, and patient representatives.

4. RARE DISEASE GROUPS

Effective translational research requires an integrated team approach. RaDaR Rare Disease Group (RDG) Leads are therefore required to openly recruit group members so that the RDG fairly represents national expertise for the condition. This includes at least one trainee, nurse, clinical and non-clinical expert and patient representative. The RDG Leads should attempt to recruit members from all devolved nations and all applicable disciplines.

The purpose of each group is to promote and 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**.**

A list of current conditions and groups can be viewed here: Rare Disease Groups | The UK Kidney Association.

Any UK based nephrologist wishing to use RaDaR to investigate a specific rare disease is invited to apply to form an RDG. New RDG applications are first reviewed by the OMG before reaching the RDC for final approval. Once approved, RDG Leads are required to sign a contract and comply with the requirements set out within it. The RDC can suspend access to RaDaR if the group does not abide by its contractual requirements.

5. PATIENT INFORMATION

5.1 Eligibility

RaDaR recruits both children and adults of all ages.

The inclusion and exclusion criteria for each condition currently represented within RaDaR can be seen here: RaDaR Inclusion / Exclusion criteria | The UK Kidney Association.

Whilst nearly all the conditions covered by RaDaR have definite renal involvement (current or potential) other cohorts are also required to fulfil RaDaR's aims. For example, healthy individuals, study control cohorts or family groups for genomic studies.

RaDaR is predominately aimed at UK patients; however international recruits who are consented in the UK by an NHS hospital are also eligible, subject to local approval.

5.2 Approach and Consent

See Table 1. Summary of recruitment documents provided and Figure 1. Recruitment flow chart.

Children – Patients aged 0-15

Patients under the age of 16 can be recruited with their parent/guardian's consent. Age-appropriate information is provided for younger children (6-11) and older children (12-15).

"Assent" is a term used to express willingness to participate in research by persons who are too young to give informed consent (under 16) but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as subjects. The patient's nephrologist or member of the clinical care team must make an informed judgment to determine when seeking assent is appropriate; the age of a child can only be taken as a guide. Where age appropriate, children and young people up to the age of 15 are asked for their verbal assent. The provision of assent is recorded on the parent/guardian consent form.

15 turning 16
Participants already recruited but turning 16 are asked to agree to ongoing participation by signing an adult (16+) consent form. Any person reaching the age of 19 that has not signed an adult form will have their data collection paused until this is addressed.

Adults – Patients aged 16+
Common law presumes that young people aged between 16 and 18 are usually competent to give consent to treatment and therefore research. Information will be offered in the patient's first language using translation services provided locally within the NHS where these are available. Written consent is obtained by the patient's nephrologist or a member of their clinical care team. Consent can be obtained in person, via post, or electronically providing that the patient has suitable opportunity to ask questions and discuss any concerns they may have with a member of the research team. Copies of the consent documents are stored in the patient's hospital record. Confirmation that consent has been obtained forms part of the data entry process.

Patients lacking capacity
Patients lacking capacity are already a massively disadvantaged group and should be afforded the same chance of having novel and advanced treatments made available. Excluding them from RaDaR would severely limit this possibility. We have therefore sought additional permissions to include them.

In some rare kidney disease cohorts, there are a significant number of patients lacking capacity. For example, research has found that people with Tuberous Sclerosis Complex are likely to experience difficulty with language acquisition, memory, information processing, attention, and organization.

The Mental Capacity Act 2005 applies to England and Wales. In Northern Ireland, the inclusion of adults lacking capacity in research is governed by the Section 132 provisions of the Mental Capacity Act (Northern Ireland) 2016. As the acts that apply in Northern Ireland, England and Wales are closely aligned, a scheme of mutual recognition of NHS/HSC research ethics committee (REC) review for research involving adults lacking capacity to consent has been agreed between these three nations. In Scotland, the inclusion of adults lacking capacity in research is governed by the provisions of Section 51 of the Adults with Incapacity (Scotland) Act 2000.

For England, Wales and Ireland a consultee must be consulted and a declaration form signed on behalf of the patient lacking capacity. The consultee should be someone who knows the person who lacks capacity well but is not acting in a professional or paid capacity (a personal consultee). An approved invitation letter, information sheet and declaration form has been provided for this purpose.

For Scotland, the nearest relative, guardian or welfare attorney must consent on behalf of any patient lacking capacity. An approved invitation letter, information sheet and declaration form has been provided for this purpose.

If a participant with capacity loses capacity during their time in RaDaR, the local study team should consult a consultee (England, Wales and Northern Ireland) or nearest relative/guardian or welfare attorney (Scotland). Relevant forms must be completed for the participation to continue.

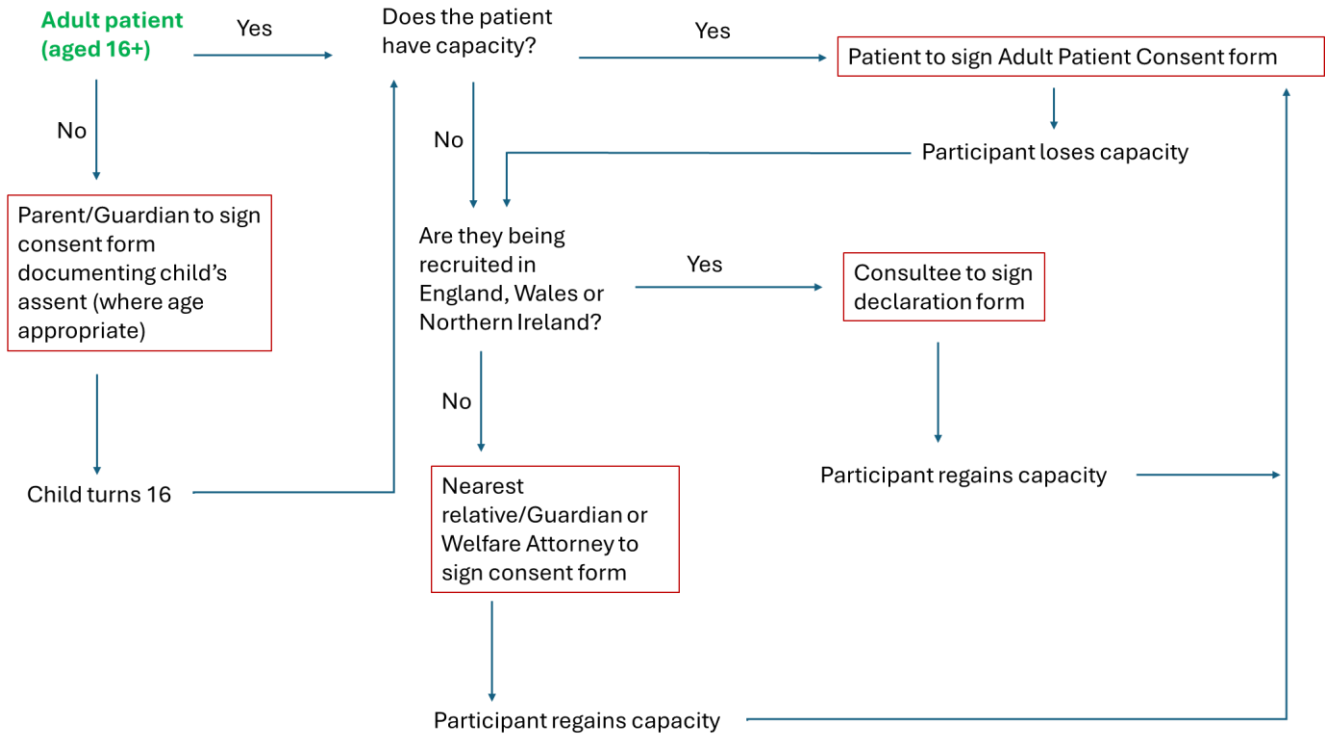
If a participant regains capacity during their time in RaDaR, they must be asked to provide their own written consent to continue participation.

Consent is not a single point in time rather an ongoing process. All participants should be asked at every visit if they are happy to continue participation in RaDaR.

Table 1. Summary of recruitment documents provided

Age	Invitation letter	Information sheet(s)	Consent
First approach Child age 0-15	Parent_Guardian	Parent_Guardian Child (age 6-11) Child (age 12-15)	Parent_Guardian *(consent form asks for confirmation of verbal assent where age appropriate)*
First approach Adult age 16+ with capacity	Adult (16+)	Adult (16+)	Adult (16+)
First approach Adult age 16+ lacking capacity England/Wales/ N.Ireland	Consultee	Consultee	Consultee
First approach Adult age 16+ lacking capacity Scotland only	Relative_Guardian_Attorney	Relative_Guardian_Attorney	Relative_Guardian_Attorney
Already consented 15 turning 16	Child to Adult	Adult (16+)	Adult (16+) *To be signed before 19th birthday or data collection will be paused.*

Figure 1. Recruitment flow chart



5.3 Withdrawal

Patients may withdraw from RaDaR at any time by notifying the RaDaR team in writing or by contacting their nephrologist/clinical care team. Their information will no longer be updated, and they will not be contacted in the future. Any existing data will remain in RaDaR to validate historical research and support ongoing/future research but no further data will be collected.

5.4 Ongoing patient contact

Once consented to RaDaR, patients may be contacted by a member of the central RaDaR team or the Rare Disease Group lead for their condition.

Contact may be by post, email or SMS and for reasons including (but not limited to):

- Invitations to attend patient information days.
- Details of further research studies that the patient may be eligible to join.
- Requests to re-consent to RaDaR following subsequent amendments.
- Patient Newsletters.
- Research Surveys.
- Contact detail checks.

Guidance on, and the process for, contacting patients is outlined in a Standard Operating Procedure/working instruction. All communications are reviewed and approved by the RaDaR Operations Manager or UKKA Senior Project Manager.

6. DATA

RaDaR provides an infrastructure to capture both generic and disease-specific clinical information and to collate longitudinal information. A key source of data for RaDaR is from the UK kidney centres who supply a daily feed of data patient data into the UK Kidney Association's (UKKA) data warehouse (the UK Renal Data Collaboration (UKRDC)) which in turn is fed into RaDaR for its consented participants, and the UK Renal Registry (UKRR) for its audit and research functions (UKRR data is collected under secondary use permissions such as those provided under s251 of NHS Act 2006). The UKRDC feed also provides data for electronic health records, such as Patients Know Best, where patients have consented for it do so.

RaDaR captures patient identifiers. This is justified by the intention of RaDaR to contact patients for a range of purposes (see section 5.4). Patients consent for identifiers to be used to collect data from key sources including:

- UKRR - data on patients with chronic kidney disease stage 3 and above and those who are receiving kidney replacement therapy.
- NHS England Hospital Episode Statistics (HES) - this includes information about all hospital admissions, including when, why and for how long they happen. Equivalent systems to HES exist in Wales (Patient Episode Database for Wales, PEDW), Scotland (Information Services Division Scotland, ISD) and Northern Ireland (Health and Social care services Northern Ireland, HSNI).
- Office of National Statistics - this includes information on patients who have died, including the date and cause of death.
- Genomics England and UK genomic centres.
- NHS Blood and Transplant (via the UKRR).

- Patients Know Best – primary and secondary care data.
- Patient reported data e.g. via surveys.
- Any UK-based approved national research studies, registries or biobanking schemes that the patient has previously consented to and participated in or will do so in the future.

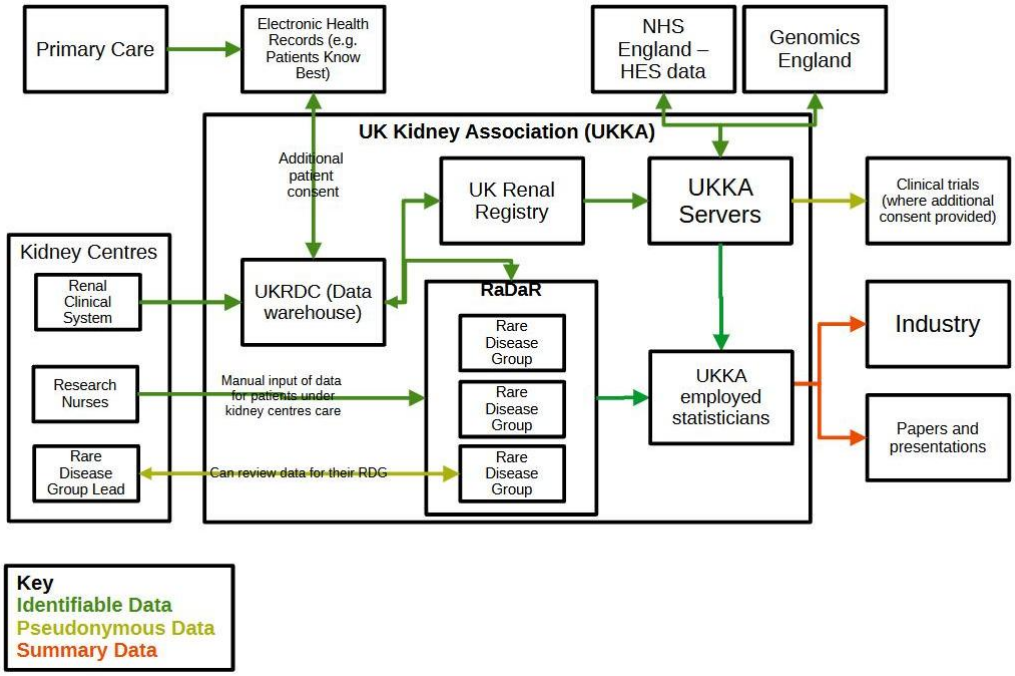
By joining RaDaR, patients give permission for researchers to use their past, present and future clinical data for ongoing and future research into kidney disease and related conditions.

RaDaR is web-based, and data is held on a secure server. The quality of data entered is the responsibility of the clinician with responsibility for the patient - usually their nephrologist or the hospital's RaDaR Principal Investigator. Many centres have research staff who perform data entry tasks.

For the avoidance of doubt, the UKRR, UKRDC, and RaDaR are operated by the UKKA (legal entity: Renal Association), which acts as Data Controller for the data flows of all three operations. All UKKA databases, network shares, and web services are held on servers hosted by Arrow Business Communications Ltd. Arrow have both ISO27011 and Data Security and Protection Toolkit accreditation. Reviews and audits of these services are carried out by the UKKA's Systems Administrator on a regular basis and monitored by the UKKA's Data Protection Officer. All UKKA staff receive regular information governance training including the appropriate use of data. Access to data is managed on an individual basis, based on the requirements of each employee's respective job roles and responsibilities. These requirements are reviewed on a regular basis in line with UKKA's Information Security Policy.

The data flows described in this protocol (see also Figure 2) are communicated to patients via the UKKA's website, including but not limited to a patient privacy notice. This privacy notice also explains patients' rights regarding their data and how to exercise them.

Figure 2. UKKA data flows



7. DATA USE AND SHARING

RaDaR welcomes applications from employees of academic, clinical and commercial organisations who would like to include analyses of RaDaR data in their research and/or collaborate with the RaDaR on grant applications. All calculations of data completeness and statistical analyses are conducted by substantive employees of the UKKA who then share the results with successful applicants. Data held within the RaDaR database are not permitted to leave the UKKA's servers. RDG Leads are permitted access to pseudonymised data for patients within their RDG. Full applications for analyses must be approved by the Lead Clinician of the relevant RDG.

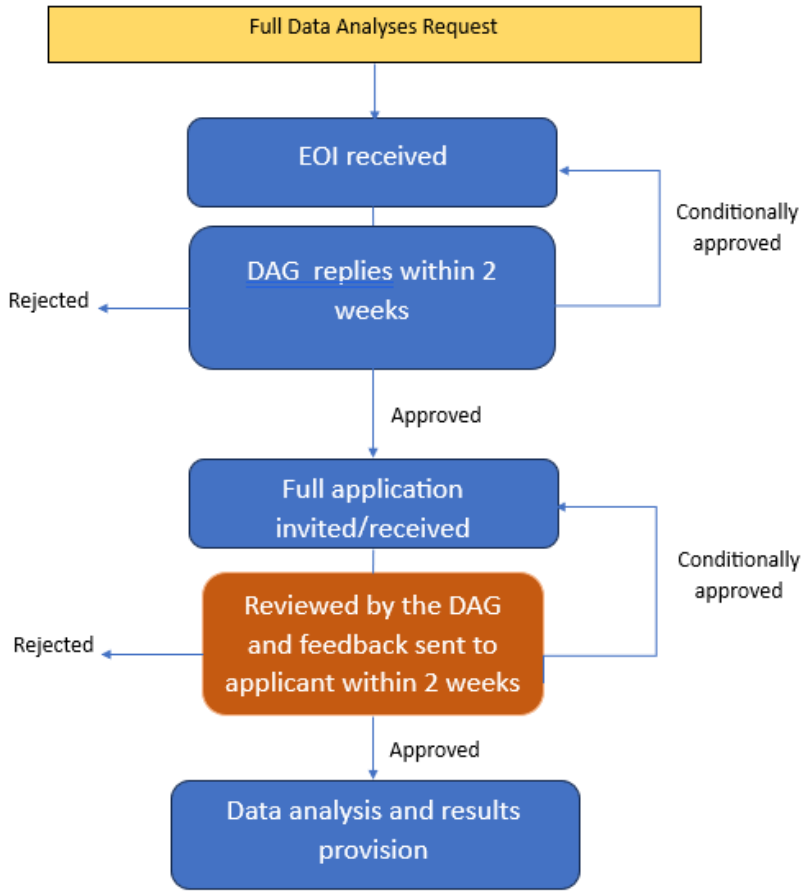
We offer two types of analysis:

1. Restricted data analysis (e.g. queries on data completeness/quality basic statistical analyses up to a maximum of 2 tables or figures, or 1 of each).

2. Full data analysis (e.g. statistical analyses >2 tables or figures, support for grant applications and quotes

The application/approval process for full data analysis can be seen in Figure 3.

Figure 3. The process for full data analysis applications/approval.



DAG: Data Analysis Group, EOI: Expression of Interest

Metadata for rare disease cohorts is available on the public facing webpage RaDaR metadata | The UK Kidney Association. The RaDaR data dictionary is also available publicly: RaDaR database | The UK Kidney Association.

7.1 The Data Analysis Group

All applications for full analyses are assessed by the DAG, apart from those where it is identified prior to the DAG meeting that there is a conflict of interest or that expertise outside that of the DAG's members is required. In these instances, the application is sent to an external peer reviewer and that person's comments are shared when that application is discussed at the DAG. Any application for paediatric data must involve the input of a clinical expert in paediatric nephrology.

The membership of the DAG includes the following people, and a meeting is only considered quorate if those marked with an asterix are in attendance.

- *UK Kidney Association's (UKKA's) Co-Medical Director (CHAIR)
  If the chair is unable to attend, this role can be delegated to the co-medical director or one of the RaDaR Directors.
- *RaDaR Director(s) – at least one should be present to be quorate
- *UKKA Director of Informatics Research/Co-Medical Director
- *UKKA Information Governance and Data Protection Officer
- *UKKA Head of Operations
- *UKKA Senior Project Manager
- RaDaR Senior Statistician
- RaDaR Operations Manager
- RaDaR Senior Data Manager
- A member of the UKKA IT/Systems team
- UKKA Head of Finance
- *British Association for Paediatric Nephrology representative – essential only if the application being reviewed involves children
- *Patient Representatives – at least one should be present to be quorate

Whilst a non-quorate meeting can still take place to allow focussed time to discuss applications, NO decisions are made until all quorate members have sent feedback to the group, this has been collated, and the response to the applicant has been approved by all members.

Using information submitted on the application form, members of the DAG discuss the scientific and methodological merits of each application and assess the level of risk for patient re-identification. The Chair leads the discussion about each application and completes an assessment form. The discussions end with a vote, which must include input from all teams that make up the DAG and at least one patient representative.
Applications are either rejected, conditionally approved, or approved.

7.2 Industry applicants

RaDaR has and continues to be a true success, making the UK a chosen place for the pharmaceutical industry to undertake research. This has enabled the establishment of a significant team supporting rare disease research based in the registry. Acknowledging that commercial applications require more rigorous consideration and can be sensitive in nature, a separate subgroup has been convened to manage these applications in separate dedicated meetings.

8. ETHICS

RaDaR has received ethical approval from the South West – Central Bristol Research Ethics Committee, reference number 19/SW/0173. Renewal is required every 5 years.

External studies wishing to recruit RaDaR patients or include individual patient information held in RaDaR must, without exception, have their own ethics approval and patient consent to do so.

9. PATIENT INVOLVEMENT

The inclusion of a patient/patient group representative is mandatory for all Rare Disease Groups, affording RaDaR a large pool of collaborative patients. In addition, up to 4 kidney patients attend each DAG meeting, with one specifically representing patients with rare kidney disease. All are additionally members of the UKKA Patient Council so have a larger patient group with whom they can discuss items and seek support.

DAG patient representatives are asked to comment on every expression of interest (EOI) received (by email) and to review full applications alongside the rest of the group at each face-to-face meeting. Lay summaries are provided in all cases. These patients have shaped our application and approval process and associated forms.

Patient representatives are also invited to review lay summaries of publication planners for upcoming publications using RaDaR data, and the results for internal projects.

A RaDaR newsletter is sent to patients twice a year. Each newsletter invites feedback from all recipients on all aspects including data collection and use and future plans/priorities.

10. FUNDING

The set-up costs and the first 3 years of operation were funded by grants from the Medical Research Council, Kidney Research UK and the British Kidney Patient Association, now known as Kidney Care UK. The Medical Research Council-grant funded paediatric cohort development of two diseases - nephrotic syndrome with focal segmental glomerulosclerosis (SRNS) and mesangiocapillary glomerulonephritis (MPGN). This permitted the setting up not only of the generic registry but also the first two Rare Disease Groups. RaDaR continues to be developed, maintained and supported by the UK Kidney Association with over £1m to date invested by the charity. Charities and others continue to provide further funding for project work and annual funding to maintain the registry on the National Institute of Health Research portfolio.

11. REFERENCES

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12. ABBREVIATIONS

AVP	Academic Vice President
CEO	Chief Executive Officer
DAG	Data Analysis Group
EOI	Expression of Interest
HES	Hospital Episode Statistics
OMG	Operational Management Group
RaDaR	National Registry of Rare Kidney Diseases
RDC	Rare Disease Committee
RDG	Rare Disease Group
REC	Research Ethics Committee
UKKA	UK Kidney Association
UKRDC	UK Renal Data Collaboration
UKRR	UK Renal Registry