Research in Renal Units
(and the UK Renal Research Network)

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Outline

- Research network structure
- Study development and delivery
- Renal Research Strategy
- Interaction with Industry
- Interaction with related specialties, NIHR/HTA
- Opportunities for trainees: NephWork
- Patient and public involvement and engagement
- Embedding a clinical research programme into a renal service
UK Renal Research network structure and study development
Study development: UK Kidney Research Consortium (UKKRC)

- Hosted by the Renal Association, Kidney Research UK (KRUK) and the British Renal Society

- **Mandate**
  - To facilitate the best research for health in kidney disease
  - To foster translational research
  - To foster excellence in kidney research in specific areas

- Very few RCTs in Nephrology
- Very few initiated and led by the UK
- Major gaps in evidence base
- Small studies/trials being undertaken by individuals – often no co-ordination with others
- KRUK, RA Clinical Trials committee and UKKRC recommended formation of **Clinical Study Groups (CSGs)** in 2009
Current Renal clinical Study Groups

- Acute Kidney Injury
- Anaemia
- CKD-Mineral and Bone Disease
- Cardio Renal
- CKD progression/biomarkers
- Transplantation
- Cystic diseases
- Exercise
- Glomerulonephritis/Vasculitis
- Haemodialysis
- Paediatrics
- Peritoneal dialysis

Rare Diseases group (RaDaR)

2 (3) cross-cutting research networks

- Renal imaging
- Clinical trials
- Big data/epidemiology*

(proposed)*
Function and purpose of the CSGs

• Understand/brainstorm the evidence gaps in the sub-specialty area
• Choose 3-5 key areas to develop
• Study design – with collaboration from several centres:
  – Multi-centre → Larger patient sample → more chance of meaningful and successful study
  – More attractive to *industry funders* (or charity eg Kidney Research UK)
• Apply for funding
Rare Kidney Diseases
An integrated strategy for patients in the UK
Renal Association and British Association for Paediatric Nephrology

“A vision for improving standards of care and equality of access for patients with rare kidney diseases” 2010

• Development of disease specific working groups
• Development of care pathways
• Development of a UK Registry for Rare Kidney Diseases
Recruiting RDGs (Oct 2018)

- Adenine Phosphoribosyltransferase Deficiency (APRT-D)
- Alport Syndrome
- Atypical Haemolytic Uraemic Syndrome (aHUS)
- Autosomal Dominant Polycystic Kidney Disease (ADPKD)
- Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)
- Autosomal Recessive Polycystic Kidney Disease (ARPKD)
- Bartters Syndrome
- C3 Glomerulopathy
- Calciphylaxis
- Cystinosis
- Cystinuria
- Dense Deposit Disease (DDD)
- Dent Disease
- Epilepsy, Ataxia, Sensorineural deafness, Tubulopathy Syndrome (EAST)
- Fabry Disease
- Fibromuscular Dysplasia
- Gitelman Syndrome
- Hepatocyte Nuclear Factor-1 Beta Mutations (HNF1B)
- Hyperuricaemic Nephropathy
- IgA Nephropathy
- Liddle Syndrome
- Lowe Syndrome
- Membranous Nephropathy
- Membranoproliferative Glomerulonephritis (MPGN)
- Medullary Cystic Kidney Disease
- Monoclonal Gammopathy of Renal Significance (MGRS)
- Pregnancy and Chronic Kidney Disease
- Primary Hyperoxaluria
- Pure Red Cell Aplasia
- Retroperitoneal Fibrosis
- Shiga Toxin Associated Haemolytic Uraemic Syndrome (HUS)
- Steroid Resistant Nephrotic Syndrome (SRNS)
- Steroid Sensitive Nephrotic Syndrome (SSNS)
- Thin Basement Membrane Nephropathy
- Tuberous Sclerosis
- Vasculitis
UK Renal Research Strategy: published 2016

- 4 strategic aims
  1. Increase engagement of professionals, patients and public
  2. Well balanced portfolio; all research methodologies; prevention, treatment and impact
  3. Support research training and career development
  4. Open culture to encourage collaboration and cross-disciplinary research
### THEME 1: Patient participation – at the centre of research progress

**Outcome measure:** Increased opportunities to participate in research (awareness, recruitment, consent, design, influence, communicate and disseminate) including minority groups (BAME, children)

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**Renal Patient Involvement and Participation Network:**
- Consent for contact (UKRR and RAdAR)
- National register of renal research participants (cf UK CT Gateway, SHARE)
- Research patient days (KRU and BKPA)
- Aims: quality improvement, practice and policy, develop quality standards, share best practice, database of patient involvement and network of groups
- Look at Health Research Authority database re a renal research hub
- Develop guidelines for recruiting BAME patients
- Lay summaries – sense check, comment and disseminate (involve CSGs and national studies)
- Guidance on reimbursement and code of practice for patients involved in studies
- Research priority survey (KRU and BKPA) – encourage participants as research advocates
- Patients on CSGs and study groups, KRU LAC, BKPA and UKRR patient advisory groups, BRU/BKPA Research Committee and BAPN Executive
- KRU LAC members visiting research institutions
- Social Media
  - To increase awareness of opportunities (eg BISTRO study)
  - KRU working with UK Renal Research on social media toolkit to increase research awareness and communicate outcomes
  - Engagement with BAME and ‘at-risk’ communities (eg KRU Peer Educator programme review, BAME participation in BRU/BKPA research)
- Communicating lay outcomes of research
  - Embedded in funding models for KRU directed research
  - Dissemination funds included in BRU/BKPA research projects
Research Study delivery : NIHR CRN
Study delivery via National Institute of Health Research Comprehensive research network (NIHR CRN)

Similar structure in Scotland, Wales and Northern Ireland (devolved nations)
NIHR CRN: Specialties, Themes and Research Delivery Divisions

NIHR CRN THEME DIRECTORS

- Cancer
- Diabetes, metabolic and endocrine disorders, renal
- Stroke and cardiovascular disease
- Children
- Genetics, haematology, ageing health and childbirth
- DeNDRoN and neurology
- Mental health
- Primary care, age and ageing; dentistry, HSR; public health
- Dermatology, musculoskeletal disorders
- Anaesthesia/per-operative; critical care, injuries/emergencies, surgery
- ENT, infectious diseases/microbiology, ophthalmology, respiratory
- Gastroenterology and hepatology

RESEARCH DELIVERY DIRECTORS - IN DIVISIONS

- Cancer
- Diabetes, stroke, cardiovascular disease metabolic and endocrine disorders, renal
- Children, genetics, haematology, paediatrics, reproductive health and childbirth
- DeNDRoN, mental health and neurology
- Primary Care, age and ageing; dentistry, HSR; public health, musculoskeletal, dermatology
- Anaesthesia/per-operative medicine and pain management; critical care, injuries/emergencies, surgery
- ENT, infectious diseases/microbiology, ophthalmology, respiratory, gastroenterology, hepatology

NIHR CRN NATIONAL SPECIALTY LEADS

- Cancer
- Diabetes
- Stroke
- Paediatrics
- Genetics
- DeNDRoN
- Mental health
- Primary care
- Musculoskeletal disorders
- Anaesthesia, per-operative medicine & pain management
- Ear, nose and throat
- Gastroenterology
- Cardiovascular diseases
- Reproductive health and childbirth
- Haematology
- Neurology
- Age and ageing
- Dentistry
- Health services research
- Public health
- Critical care
- Infectious diseases and microbiology
- Ophthalmology
- Hepatology
- Injuries and emergencies
- Ophthalmology
- Surgery
- Respiratory

LOCAL CLINICAL RESEARCH NETWORK

RESEARCH DELIVERY MANAGERS - IN DIVISIONS

- Cancer
- Diabetes, stroke, cardiovascular disease metabolic and endocrine disorders, renal
- Children, genetics, haematology, paediatrics, reproductive health and childbirth
- DeNDRoN, mental health and neurology
- Primary Care, age and ageing; dentistry, HSR; public health, musculoskeletal, dermatology
- Anaesthesia/per-operative medicine and pain management; critical care, injuries/emergencies, surgery
- ENT, infectious diseases/microbiology, ophthalmology, respiratory, gastroenterology, hepatology

LOCAL SPECIALTY GROUPS

RESEARCH DELIVERY WORKFORCE
NIHR Renal Disorders group: trial delivery (£4 million + funding each year)

- Expanding the renal portfolio: 62 studies in 2008; now >100
- ‘Medical’ urology is included in the Renal Disorders portfolio
- Funding is used for research nurses and trials assistants, research administrators, for research fellow time and for the specialist to ‘buy out’ clinical time to devote to research
- Commercial study funding provides opportunity to grow the local team by using commercially generated income to fund further research nurses or research fellows

Assessment

- RAG: ‘green’ at study closure is the key metric → Diligent portfolio management
Combining strengths: Collaboration with stakeholders

Close and unique working with:

- Kidney Research UK (KRUK)
- UK Kidney Research Consortium (UKKRC)
- Patient groups
- Industry
- NIHR CRN
- Other specialties

Renal CSG structure now replicated in Cardiology and Diabetes
Acquisition of funding for large trials: several models
Example of collaborative trial design: development of the PIVOTAL study

- Anaemia CSG recognised an issue with iv iron use in haemodialysis patients – developed an RCT
- KRUK engaged with Pharma: Vifor – Fresenius provided grant (now £3.5 million)
- Clinical Trials Unit: Glasgow appointed Feb 2012
- Protocol developed: 2080 patient sample size
- UK nephrologists consulted regarding the rationale and outline at national meeting in Newcastle (June 2012)
- Trial launched November 2013

Industry → KRUK → UKKRC → trial → CRN (delivery)
Associations between IV iron dose and mortality

Hazard Ratio (95% CI)

HR for ACM per 100 mg/mo higher = 1.02 (95% CI = 1.00-1.05), p = 0.05

- All-cause mortality (ACM)
- CV related mortality (CVM)
- Infection related mortality (IM)

Average Monthly IV Iron Dose (mg/mo)

- 0 (35 observations)
- 1-99 (13 observations)
- 100-199 (21 observations)
- 200-299 (17 observations)
- 300-399 (5 observations)
- ≥400 (9 observations)
Ferritin and IV Iron Use in DOPPS

Mean Serum Ferritin (ng/mL)

Mean IV Iron Dose (mg/month)

Trial Design

Proactive, high-dose IV iron arm (n=1093)
IV iron 400 mg/month (withhold if ferritin >700 µg/L; TSAT >40%)

Reactive, low-dose IV iron arm (n=1048)
IV iron only administered if ferritin <200 µg/L or TSAT <20%

≥631 primary endpoint events (i.e., all-cause mortality, MI, stroke, or HF hospitalization)

Screening:
≤4 weeks

Follow-up period with monthly visits

Median (maximum) follow-up: 2.1 (4.4) years

HD=hemodialysis; HF=heart failure; MI=myocardial infarction; TSAT=transferrin saturation.
Network of Sites

**England**
Queen Elizabeth Hospital, **Birmingham**; Heartlands Hospital, **Birmingham**; Royal Free, **London**; King’s College Hospital, **London**; Guy’s & St Thomas’, **London**; St Helier, **Surrey**; St George’s, **London**; Royal Liverpool Hospital, University Hospital Aintree; Sheffield Teaching Hospital; Lister Hospital, Stevenage; Salford Royal Hospital, Manchester; Manchester Royal Hospital; Queen Alexandra Hospital, Portsmouth; Kent & Canterbury Hospital, Leicester General Hospital, Hull Royal Infirmary; Freeman Hospital, Newcastle; Churchill Hospital, Oxford; University Hospital of North Staffordshire, Stoke-on-Trent; Southmead Hospital, Bristol; Royal Cornwall Hospital; Nottingham City Hospital; Norfolk & Norwich Hospital; New Cross Hospital, Wolverhampton; Royal London Hospital; Wirral University Teaching Hospital; Royal Shrewsbury Hospital, Royal Devon & Exeter Hospital, Royal Preston Hospital, St James’ Hospital, Leeds; Hammersmith Hospital, London, Royal Sussex Hospital, Brighton; Bradford Teaching Hospital; Coventry University Hospital; Southend University Hospital; Gloucestershire Royal Hospital; Derriford Hospital, Plymouth; Royal Berkshire, Reading

**Wales**
Morriston Hospital, Swansea; University Hospital, Cardiff

**Scotland**
Western Infirmary, Glasgow; Victoria Hospital, Kirkcaldy; Ninewells Hospital, Dundee; Royal Edinburgh Hospital

**N. Ireland**
Belfast City Hospital, Antrim Area Hospital; Daisy Hill Hospital, Newry; Altnagelvin Hospital, Derry
Death, MI, Stroke, or HF Hospitalization (Primary Endpoint)

Hazard ratio, 0.85 (95% CI, 0.73–1.00)
Noninferiority $P<0.001$
Superiority $P=0.04$

Hazard ratio (95% CI) adjusted for stratification variables: vascular access, diabetic status, and time on dialysis; $P$ value from Wald test.
Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

16 UK centres; sample size 3000 CKD Patients (eGFR < 60 ml/min or 60 ml/min but uACR > 30 g/mol)
100 controls
Biobanking; renal biopsy in 25%; UK Renal registry data linkage
£3 million funding from 3 large Pharma companies
Increasing the number of Commissioned Nephrology calls from HTA

- Phosphate lowering in non-dialysis CKD: not awarded
- Cystatin C as a marker of GFR: awarded (eGFR study)
- Bicarbonate treatment in elderly CKD with acidosis: awarded (BICARB)
- Exercise on dialysis: awarded (PEDAL)
- Renal nerve ablation therapy (multi-specialty; led by BHS): not awarded
- PEXIVAS: awarded: awarded
- Extended duration haemodialysis: awarded

Now regular interaction with NIHR programme managers; encouraging applications and topic suggestions
Three systematic reviews found no evidence of superiority of HDF over HD

- NIHR funded H4RT to answer the question (£1.5m)
- Horizon 2020 funded CONVINCE to answer the questions (€7m)

The NICE draft recommendation (that there was evidence of superiority of HDF over HD and that HDF should be offer to all people dialysing via vascular access) was challenged by:

- The Renal Association
- The British Renal Society
- Cochrane Renal Group
25 sites recruiting

Aberdeen  London, Guys St T
Bradford  London, Royal Free
Bristol  Manchester
Canterbury  Newcastle
Cornwall  North Midlands
Coventry  Nottingham
Dundee  Plymouth
Edinburgh  Salford
Glasgow  Sheffield
Ipswich  South Tees
Kirkcaldy  Stevenage
Leicester  Sunderland
London, Barts  Portsmouth

Joining soon: Liverpool

Contact:
H4RT-study@bristol.ac.uk
Fergus.Caskey@bristol.ac.uk

716/ 1550
46%
(end April 2019)
Research collaboration with other specialties
Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D., Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D., Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,* Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D., Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D., Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D., Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D., for the FAIR-HF Trial Investigators†
• Partnership of Cardio-Renal CSG with BHF heart failure CSG
• Inclusion : high-risk HF (hospitalisation within last 6 months; EF < 45%; BNP > 150); iron deficiency
• Primary end-pt : composite of CVS mortality and CVS hospitalisation
• Sample size : 1300 patients; > 60 UK sites
• Safety end-point : all cause mortality; all cause hospitalisation; infections
• Partnership funding £3.5 million from BHF (£1.8 million) and Pharmacosmos
• Commenced April 2016; current recruitment 700 patients
Trainee involvement in research

- Trainees encouraged to align themselves with appropriate Clinical Study groups (CSGs)
- Following ‘StarSurg’ model: creation of the ‘NephWork’
- Currently developing a UK wide AKI audit: 10 years post-NCEPOD AKI report
- Will involve most renal centres in the UK; support from the Renal Association
- Led by SpRs: credited with publication etc
Patient and Public Involvement and Engagement strategy (PPIE)

Goal of NIHR to improve PPIE

- Developing tool kits for improving communication with patients and carers for use at individual sites
- Appropriate patient representation on the CRN Renal Disorders group
- Emphasis on early stage involvement of patients and carers at study development stage
Patient events and Newsletters

Kidney Research—An Opportunity For You To Make A Difference!

Welcome to the second edition of the kidney research newsletter! We have been really busy over the winter months introducing new studies to our already extensive portfolio. Freddy would like to thank all the patients who have taken part in our research over 2013. We have recruited 417 patients to a range of studies over last year which is a fantastic effort from our Renal Research Teams and of course the patients who volunteered to participate in research studies.

If you have kidney disease, you may be able to help out and be a part of exciting research projects taking place at Salford Royal Hospital NHS Foundation Trust. We are always looking for volunteers and without patients we would not be able to carry out the research at all.

What are the benefits for you in taking part in research? Some studies may of direct benefit to you depending on what treatment is being tested. With other studies, the results will certainly help change practice and affect management of patients with kidney disease like you. This means that you might be helping yourself and others.

If you are involved in research you will be monitored closely by the research teams and so you will receive extra attention in addition to general clinical care.

See elsewhere for further information about studies that are on-going in our renal department at the moment. Also information about how studies are progressing so far. Participation is voluntary. If you are interested please contact the research teams.

Kidney Patients’ Research Day—Enjoyable and Informative

Our first Kidney Patients’ Research day in December 2013 at the de Vere White Hotel, Reebok Stadium, Bolton was a great success with over 100 attendees—many were kidney patients and carers who were interested in finding out more about kidney research. Thank you to all the speakers who made the day successful.

We discussed what our renal research studies are available to patients treated by Salford Royal NHS Foundation Trust, the progress in studies so far and how research successes have led to improved care and quality of life for all patients. Some patients also came to share their own experiences of participation in research which was very positive. Michael Nadin from Kidney Research UK (KRUNA) also came to talk about KRUNA and patient involvement.

To those of you who are interested in finding out more about renal research, the research teams will be happy to answer your questions.

Kidney Research Studies—A Chance to Take Part!

There are many studies ongoing at the moment which are available to kidney patients whether you have CRF, a functioning transplant or receive dialysis. Here are just a few examples:

BICARB

Bicarbonate is commonly found in foods such as baking powder. It is also present in the body controlling how acidic our blood is. When kidneys do not work so well, our ability to control bicarbonate levels in the blood falls and the blood may become more acidic. This medical research is for people aged over 65 years who have chronic kidney disease. It asks the important question of does sodium bicarbonate therapy improve function and quality of life in older patients with chronic kidney disease (CKD) and low-grade acidosis? Recruited patients are randomized to take place of bicarbonate or placebo.

If interested please contact: Janet Blood Tel: 0161 206 5205 Email: Janet.Blood@salfordimaging.nhs.uk

Chronic Renal Insufficiency Standards—Kidney Research (CRIS-KID Study)

This study investigates whether it is possible to use routine bedside tests to determine heart amyloidosis and electrical activity in order to predict heart events in patients undergoing hemodialysis. Recruitment finished in March 2014. There were 230 patients who received a dual sensor patch and had blood and urine samples taken.

Full data collection was on-going at present. So watch this space!

CSD-CRT

Cardiac Synchronous Damping—Kidney Research Study (CSD-CRT Study)

We are using technology that controls the blood flow of patients during dialysis. This is because there are evidence regarding higher levels of blood flow with poor outcomes.

Kidney Research—How Studies Are Progressing

The chronic renal insufficiency standard is an implementation study of hemodialysis. Recruitment finished in March 2014. There were 28 patients who agreed to participate from Salford, Bolton, Wigan and Ecclesdale.

Full data collection is on-going at present. So watch this space!

Severe Phosphate Intervention in Renal Replacement Therapy (SPIRT Study)

We are using technology to control the blood flow of patients during dialysis. This is because there are evidence regarding higher levels of blood flow with poor outcomes.
Outputs of the UK Renal research network

- Designed at least 60 studies in the CSGs
- Major network funding: eg Renal Imaging network - MRC infrastructure grant; MRC stratified medicine grant (NURTuRE)
- Funding from Medical Research Council; Wellcome; NIHR HTA; Kidney Research UK; British Heart Foundation
- Total funding > £38 million since the UKKRC was developed
- 2 big RCTs developed in collaboration with industry (£3.5 million each)
- More UK renal centres now involved in research (eg 50 in PIVOTAL)
- Large cadre of NIHR funded trials nurses underpinning clinical research
UK Renal Research Network: areas to improve

- Greater integration of renal basic scientists in research network activity
- Greater opportunities for trainee and other health care worker involvement in research
- **Increased awareness of the renal community about the network structure and how to get involved**
- Number of nephrologists in key charity panels (e.g., MRC, NIHR HTA, EME)
- Greater focus on PPIE with > patient awareness of research opportunity; involvement in study design
How to embed research into a clinical service
Key steps to developing renal research at your centre

- Research-interested clinicians
- Participation in clinical trials: commercial studies can bring funding to develop infrastructure (variable); national academic studies can fund trials staff
- Fund a clinical research fellow (e.g., endowments; educational grants from pharma) and develop own projects
- Encourage consultant colleagues to join a UKKRC CSG or network - expand local research enthusiasm and capacity
- Encourage SpRs to engage in NephWork
- Offer placements for Foundation level research trainees and Academic Clinical Fellows
- Interact with local University
Cardiovascular, metabolic and kidney disease: crosscutting science and best practice

Are you involved with patients who have multimorbidity?

This 1-day conference, held on 1 July 2019, will look at updates in multimorbidity and the clustering of common diseases in patients.

Evoking discussion and dialogue on ways to improve the health of these patients, the conference offers a packed programme full of informative sessions and take-home messages for direct use on the ward.

Topics covered will look at: the latest insights from industry regarding the treatment of inflammation and fibrosis; how digital health and AI are driving research on delivering