Trans-national cohorts of nephrotic syndrome – a unified approach to a global chronic disease

1. IMPORTANCE

**Kidney disease in the LMIC settings**

Renal disease in the context of LMIC (Low and Medium income countries) health settings is almost always devastating, given the extremely low number of nephrologists per capita, a paucity of diagnostic capability (specialised blood tests e.g. antibody profiles, biopsy, genetics), expensive drugs, and in particular virtually no access to care for chronic disease and ultimately dialysis and transplantation.

Idiopathic Nephrotic syndrome (INS) is one of the most common renal diseases in children and adults with the central event being glomerular podocyte injury.

INS in the developed world has an incidence of 2-7/100,000 population, and is defined as ‘rare’. However, in LMICs there is widespread anecdotal evidence that INS is a common and chronic disease, though ironically the only published epidemiological evidence comes from a study of South Asian populations in the UK1. Our partners in India for example typically report 60-100 new patients per year per centre (Bagga, Vasudevan, Vellore, pers communication). The reasons for the differences are unknown, and the morbidity and mortality from INS in countries such as India, Egypt and South Africa is considerable and worsened by frequent infectious complications. This partnership will focus on paediatric INS in 2 countries (India and Egypt) and both adult and paediatric INS in South Africa and the UK.

**Definitions**

INS is a heterogeneous and chronic disease, centred on damage to the glomerular podocyte, and treatment is largely empirical and unsuccessful, with steroids as the initial mainstay of therapy. Close to 70% of children with INS have some response to steroids and are labelled as steroid ‘sensitive’ (SSNS), and the rest as steroid ‘resistant’ (SRNS), with single gene mutations underlying 26.2% of the latter group in the UK2. The burden of morbidity is enormous, and a diagnosis of steroid resistance is especially challenging, as 50% will go on to established renal failure within 5 years, despite intensive immunosuppressive regimes.

**Clinical Picture**

Typically patients present grossly oedematous, with intravascular depletion (third-spacing of fluid), risk of infection and thrombosis. Additional long-term complications then accumulate, such as hyperlipidaemia, hypertension, hypothyroidism etc.

Disease modification requires steroids, followed often by second-line therapies such as calcineurin inhibitors and (rarely available) anti-CD20 monoclonal antibodies. Treatment algorithms in the UK are based on response, with considerable variability in use of second line agents, and in LMICs this is further complicated by lack of availability/cost, as well as considerations of infectious risks. Therefore the need for targeted stratification is vital.

Symptomatic management includes requirement for intravenous albumin infusions, anti-hypertensives and lipid lowering drugs. Chronic protein losses also lead to malnutrition. Most therapies are expensive, difficult to access, and require specialist expertise. Lack of appropriate treatment even if the child survives potentially life-threatening complications, contributes to an adverse outcome of renal scarring and end-stage renal failure – with very few individuals having access to dialysis and transplantation.

**Incidence and progression**

Single centre audits from our co-investigators in South Africa show a higher rate of steroid resistance (38.5%), and complications (41.1% rate of admission for bacterial infection), and a strikingly high rate of loss to follow up (61.6%) suggesting poor access to healthcare for this chronic condition. Mortality (given the caveat of very limited follow up) was 1.8%. A similar retrospective single centre review (unpublished) from another Johannesburg co-investigator shows 18-20 new referrals per year, 42.3% steroid resistance, rising to 50.0% in the black sub-population. Stunted growth, hypertension and reduced GFR were amongst the commonest complications, indicating both chronicity and lack of treatment efficacy.

**Stratification Potential**

Treatment algorithms for INS remain broad and non-specific, with little progress in mechanistic stratification, which would limit both unnecessary toxicity (and cost), as well as selecting the most appropriate subgroups to target with novel biologics (with a long term aim of making those available at locally sustainable budgets).

Recent advances in the field of podocyte biology have revolutionised our understanding at the molecular level3, 4, but we have only tentatively begun to translate this into therapeutic and diagnostic advances. For example we can now say that there is a large minority of INS patients with single gene disorder (one of currently 53 known causative genes) causing their condition, varying according to the ethnic population. Of the rest, the majority will have a ‘circulating factor disease’ for which we currently have no consistent biomarker, and which may be more prevalent in environments with exposure to multiple infectious triggers.

**Collaborative Translational Plan**

One of the largest gaps in translation is the study of well-characterised cohorts with INS from across different environments and ethnicities. There is an urgent need for new therapies, many already in clinical use elsewhere, to be trialled in mechanistically relevant cohorts of INS patients. Alongside this, the development of plasma and urine biomarkers is key to identification of appropriate subgroups, and to deliver the highest likelihood of success of clinical trials.

The opportunity here is to pull together enthusiastic and highly dedicated clinician/researchers from LMICs where the disease is prevalent, alongside world-leading glomerular biology and population research in the UK, as a means to accelerate clinical advances in this area at a rate not otherwise ever achieved.

The practical vision therefore, is to develop local research skills (specifically laboratory based biomarkers and epidemiological/clinical trials expertise) in the settings where the disease is most prevalent. This will also allow comparisons of disease in differing settings to understand the pathobiologies, particularly genetic and inflammatory, and use this knowledge to introduce/test the most relevant novel biomarkers and therapies

2. BACKGROUND

**The UK strengths**

Bristol Renal is a world-renowned glomerular disease research group, with over 40 researchers, an inclusive mix of clinicians (adult and paediatric) and discovery scientists. The PI established the first conditionally immortalised human podocyte5 (and other glomerular cell) cell lines, which remain the gold standard research tool worldwide.

The PI has established an *in vitro* disease model whereby human podocytes are exposed to human disease plasma, and detailed podocyte parameters can be measured as direct biomarkers of active disease6-8 . Alongside this, a collaboration with Evotec has resulted in a high throughput ‘podocyte injury assay’, which is currently being worked up for clinical utility. This means new biomarkers can be discovered and rapidly tested using established techniques, with the availability of human plasma from different stages of disease.

Alongside the laboratory advances, we have solid momentum over the last 6 years, of having established in the UK firstly a renal rare disease registry (RADAR9, http://rarerenal.org/radar-registry/), and a mature national cohort of SRNS patients in paediatrics, which has now extended to patients with SSNS (study name – NephroS). Importantly the IT is run within the established UK Renal Registry, and linked to Renal Patient View, both NHS embedded organisations, with a project underway to establish ‘International RADAR’ in order to facilitate linked international rare disease registries.

This has led to, for example, a new clinically approved test using rapidly parallel sequencing for all 53 currently known SRNS genes10 (<https://www.nbt.nhs.uk/sites/default/files/filemanager/editor/BGL%20service%20proforma%20for%20Nephrotic%20Syndrome.pdf>), and discovery of several new genes11-15.

The latest development to stem from the success of RADAR and pertinent to this application is termed NURTuRE, a national renal translational research nurse network designed to facilitate patient recruitment from across the UK, and critically to collect a comprehensive, meticulously regulated collection of patient biosamples, stored at the UK Biobank in Milton Keynes. This has attracted significant industry investment (£1.95M to date), and is seen as an exemplar of academic-industry partnership in order to advance biomarker and compound development through all stages of testing. Nephrotic Syndrome is one of the two pilot cohorts in NURTuRE, the study is termed NURTuRE-NephroS, and will recruit 1000 INS patients in the next 2 years.

**Potential of building an International Network**

There are several fundamental questions that could be addressed by the establishment of similar high quality epidemiological and biosampling infrastructure in LMICs. These include **accurate estimations of incidence, outcomes, and responses to current therapies**. More detailed study will reveal incidence of monogenic disease, effects of environment (e.g. rural/urban), nutrition, early life influences, and infectious triggers. For example Dr Kala in Johannesburg has noted that nephrotics with SRNS and Tuberculosis compared to SRNS without Tuberculosis went into renal failure much faster, and postulates a link to a hyper immune response to TB with a possible genetic susceptibility.

The funding intends to establish a **core cohort and laboratory infrastructure** in each partner country, that is able to operate independently and collaborate as part of this new network, with key links to the UK PI and cohort, and each other, for joint projects going forward. Each partner institution will employ two research nurses and a post-doctoral researcher. Bioinformatics will be progressed in the UK laboratory in collaboration with the MRC Integrated Epidemiology Unit in Bristol, alongside ongoing biomarker discovery and development.

**Novel biomarkers or genetic candidates** under investigation in the PIs lab and elsewhere can be rapidly tested in large populations, and new collaborative partnerships for substantially powered trials in biologically stratified patients utilising novel therapies will be informed by those findings.

There is a compelling need to **introduce effective new therapies** in this group of patients that will limit the severe morbidity and chronicity that typically cripples families in LMICs who cannot afford current treatment, even if available.

3. THE LMIC PARTNERSHIP AND POPULATIONS TO BE INCLUDED

The objective is to utilise world-leading initiatives in both biological techniques and application to stratified patient cohorts, to build appropriate and usable parallel research capabilities in LMICs

The proposed plan is to use the expertise Bristol has in (1) unique laboratory based biomarkers, and (2) deeply phenotyped comprehensive national patient cohorts, to transfer knowledge and skills to partner countries to set up parallel cohorts. This will extend the scope of the existing research to global settings, permitting comparative data across countries, and sufficiently powered clinical and biomarker studies to advance knowledge in a poorly understood setting.

We have established over the last 5 years partnerships between the host PI and laboratory and each of the partner countries, as groundwork for this aim:

**1. All India Institute for Medical Research (AIIMS), Delhi**. With Professor Bagga we were granted a British Council UKIERI research award (2012) to establish links between UK (Bristol), US (Ann Arbor, Michigan) and AIIMS, Delhi. This modest grant ($75k) permitted setting up of compatible patient databases, limited sample collection in Delhi, and training of PhD students and junior faculty from India in the partner facilities in UK and the US. Excitingly, this project has directly led to a **Govt. of India DBT grant over 5 years**, commencing March 2016. The aims are to collect 500 INS patients at first presentation, over 13 Indian tertiary centres, with a biorepository. Whole exome sequencing on 250 patients is funded, but with no current bioinformatics funding. A database, compatible with RADAR, is being developed. This proposal will align seamlessly here, wherein we will embed research nurse, biobanking and biomarker support, and expand cohort recruitment to include all prevalent patients. A likely outcome therefore is that this project will **leverage access to a significantly larger cohort of patients across India** that can be studied in the next phase with the same analytical platform.

The Bagga group has also established podocyte culture in their laboratory over the last 5 years, using cell lines from Bristol, and will receive further training in the more sophisticated readouts currently used in the Bristol lab.

Professor Bagga is a world-leading expert on **clinical trials in INS**, with many high profile studies that have advanced the treatment algorithms utilised worldwide16-24. This is an exemplar of how access to the extensive incident INS patient population combined with an enthusiastic and talented local chief investigator can be successfully translated in a LMIC setting to significantly advance our knowledge of the disease.

**2. St John's Medical College, Bangalore**. Dr Vasudevan initiated this collaboration by firstly utilising world leading podocyte cell lines established in the Saleem lab in his NS research. The PI visited Dr Vasudevan in 2014, to further strengthen research links, and extend the educational scope of the work. Since then the PI has mentored Dr Vasudevan, who is actively building up his laboratory (currently 3 PhD students, 1 post-doc, 2 lab technicians), for a current Wellcome - DBT and a Newton Fellowship application. The Vasudevan laboratory is therefore well primed to extend podocyte based biomarker work, and will serve as the leading biomarker hub in India to enhance training in other centres, starting with Delhi.

**3. Cairo University, Egypt.** Since 2012 the PI has taught on renal genetics and biology on courses organised by Professor Neveen Soliman, a prominent paediatric nephrologist, in Cairo. Subsequent to this, a clinical Fellow from her team was awarded a European Renal Association Fellowship to come to the PIs lab in Bristol for 2 years (2013-15), and learn glomerular genetics and cell biology techniques. This has established a strong translational research link with Professor Soliman's team, which would be propelled by the current proposal.

There are currently no cell biology/biomarker techniques established in Cairo, so the current proposal will establish the standardised protocols used in Bristol, with the advantage that the Fellow who visited Bristol (Dr Marwa Nabhan) now has an established post in the department with Prof Soliman, and can supervise this work.

**4. Johannesburg, South Africa**. A consortium led by Prof Saraladevi Naicker- one of South Africa's leading nephrologists, with whom we have recently proposed a project to build a national cohort and biobank, perform genetic analysis and examine the link between NS and TB in South Africa. This is at the stage of building the multidisciplinary collaborative network, so would be ideally boosted within this proposal. She has brought together an enthusiastic group of nephrologists for this proposal, adult and paediatric, from the tertiary centres in Johannesburg. The research nurses will be employed covering both adult and paediatric hospitals (Naicker, Kala, Levy, Paget). Two Fellows from the Naicker group have recently visited Bristol to learn laboratory podocyte techniques, and thus build experience.

Each institution already has limited local cohort collections, to varying degrees, and the coordination and organisation achievable by this project would establish a blueprint for sustainability, allowing cutting edge biomarker studies within and across populations within 3 years, and clinical trials on mechanistically stratified groups of patients within 3-5 years. This would be the first international consortium in INS established for this poorly understood and devastating disease, and has the unique novelty of bringing together countries with the highest disease prevalence with world leading laboratory and translational research.

4. KEY KNOWLEDGE GAPS, AND RESEARCH OPPORTUNITIES

1. What is the incidence of INS in these different LMIC settings, according to age; socio-economic status; geography (urban/rural); ethnicity; genetics; country differences.

2. What are the prevalent environmental triggers, particularly infectious, that could account for and aid mechanistic understanding of the immune pathogenesis

3. Which subgroups of patients, according to the above stratification, respond to first or second line immunosuppression, in their respective environments.

4. How can we stratify patients utilising novel biological and biomarker insights.

The target cell of INS is the glomerular podocyte, and podocyte biology research has exploded over the last 15 years. Major advances in genetic and biological understanding now puts clinicians and researchers at the threshold of a major reclassification of the disease, and testing of targeted therapies both identified and novel. This proposal aims to achieve exactly that potential, by partnering with LMICs for genetic analysis, deep clinical phenotyping and introduction of mechanism derived biomarkers into clinical practice. The ability to partner the world’s leading laboratory programme with the clinical settings where the disease is most prevalent presents a truly unique opportunity to join strengths that could catapult our ability to advance mechanistic understanding and thereby change disease management.

The project will establish for the first time an **international network of collaborative centres** that have demonstrated enthusiasm and considerable initiative for taking forward both clinical and scientific boundaries in INS worldwide. At the core of this will be the laboratory and clinical expertise of the host country (UK), which has established an exemplar translational pathway that can be used to inform all the key aspects of the research plan in each centre.

Once the network is embedded, an infrastructure will have been built to access the **most substantial patient cohort in the world** that will continue to exploit the rapid discoveries in podocyte biology that are generating important translational opportunities.

Research Opportunities:

There are a number of **important biomarkers**, still clinically unproven, derived from podocyte focused cell biology research in recent years that can immediately be tested on the collected cohorts. These include podocyte b125 and b326 integrin expression (on biopsies); serum soluble urokinase-type plasminogen activator receptor (suPAR)27; and podocyte VASP phosphorylation8. In this highly active field, more are likely to be implicated, and the single biggest gap in knowledge for all biomarkers to date is the ability to test them in large cohorts of well phenotyped patients.

**Immune links.** Historically, INS has been considered a T-cell mediated disease; however, evolution in basic immunology and therapies of INS e.g anti-CD20 antibodies propose a more nuanced pathogenesis with potential participation of innate immunity, B-cells, T-cells, and innate lymphoid cells (ILCs). Infectious triggers play a central role in relapse, and have been poorly studied to date. The experience of our LMIC partners clearly points to viral triggers, rather than any of the other prevalent infections present in their environments. This presents a strong and overlooked clue to immune pathogenesis, pointing to the study of immune cells related to viral activation, e.g. NK cells. This network will be able to precisely study the balance of viral/other infectious triggers causing relapse, leading to future directed studies of the immune activation profile at different disease stages.

**Genetic Architecture of INS** – see below

5. THE RESEARCH PLAN

(i) Obtain **ethical approvals** at each centre to carry out the proposed research plan, including ethics for collection of blood, urine and DNA from ethnically and age matched controls.

(ii) Establish the ability to **collect on going clinical data** in an international web-based registry, and recruit patients using an established systematic protocol applied across all centres

This will focus on 2 main practical steps:

(a) Full time Research nurse x2 at each centre – these will ensure identification and recruitment of both incident and prevalent INS patients, in-patient and out-patient.

They will implement robust (as far as possible) follow up and tracing procedures

(b) Uploading of clinical information (using and adapting existing RADAR datafields) and sample storage data to a centralised web based registry (‘International RADAR’), alongside upload of pathology laboratory data, automated as far as possible.

This is based upon the UK renal RADAR database, out of which runs the NephroS study, which recruits patients with INS. We have detailed datafields for deep clinical and laboratory phenotyping, with web based entry available to all clinicians and research nurses. All data is link-anonymised, with different levels of permissions as appropriate. This experience will be shared completely to each LMIC centre.

(iii) Establish a robust and standardised protocol for **high-quality blood and urine sampling at different stages of disease**, handling and storage, as well as biopsy material (where available). This will be identical across all sites and follow the NURTuRE-NephroS standard operating procedure, so that data can be compared.

Biosamples (blood and urine) will be spun, aliquoted and rapidly frozen Manual barcoding of all samples using pre-labelled tubes. Biopsy specimens will be stored according to NURTuRE-NephroS protocol.

(iv) Employ a post-doctoral researcher in each centre. This will set up each centre with the **ability to extract DNA and RNA** from blood samples, and with **laboratory based podocyte assays for novel biomarker development** and testing. The plan involves establishment of human podocyte cell line cultures in each lab (lines provided from Bristol as necessary). Training will be carried out on individual bases over a 4 week period by a post-doc and a technician (Mrs Lan Ni) in the UK laboratory who is highly experienced in cell culture techniques, as well as protocols for exposure of podocytes to human disease plasma, and readouts of protein localisation (by immunofluorescence microscopy); Western blotting for protein and phosphoprotein quantification; cell motility assays; cell permeability (transwell) assays. ELISA techniques for quantification of serum biomarkers will also be learnt.

This is intended to provide basic and practical laboratory techniques in each local laboratory, with the flexibility to address different questions as they arise. It will also embed the relationship between Bristol and each LMIC centre, so that future grant applications can expand on scale and sophistication of laboratory methods.

The Bristol post-doctoral researcher will establish biomarker assays and protocols, train visiting researchers, and act as overall project manager for consortium recruitment and standard operating procedures.

(v) **Train key personnel in clinical trials** (Delhi, Bristol) and **epidemiological expertise** (Bristol)

In the second year of the proposed programme, post-docs from each of the other LMIC centres will visit Delhi, to learn about clinical trial set up in the LMIC healthcare environment. This will be supplemented by a visit by the PIs to discuss forward plans for clinical trials based on the infrastructure established.

For future projects generating ‘big data’, the collaboration with Dr Tom Gaunt (MRC IEU, see above) will be used to train LMIC researchers in Bristol in world-leading bioinformatics techniques, with an aim of synchronising clinical trials with deep genetic and biomarker profiling, at the same time building sophisticated skills in each LMIC.

5. FUTURE FUNDING OPPORTUNITIES BASED ON DELIVERABLES FROM THIS PROPOSAL

Deliverables (which will make future funding applications robust):

**1. Epidemiology**

Each of the Indian centres sees approximately 250 prevalent SSNS patients per month as outpatients, so we estimate recruitment of 2-3000 patients in 2 years. This is possibly an order of magnitude greater than UK prevalence (Bristol Children’s Hospital has approximately 100 prevalent patients). South African prevalence from local audit and research data appears somewhere in between these numbers (60 new patients per year per centre), though in the absence of a denominator, figures remain approximate.

Within the timescale of this project, we will be able to: Identify ethnic and demographic patterns of disease, establish a clearer incidence in different populations, and investigate patterns of disease, e.g steroid resistance, dependence, familial incidence. We will also investigate links to infectious and other environmental triggers in the different environments.

At an early stage of analysis, applications will be made for funding for widespread genetic analyses on the collected cohorts, which will quickly permit population stratification according to genetic and non-genetic disease mechanisms, and establish local ethnically appropriate control populations to accurately analyse disease causing candidate variants and permit genome wide association studies to understand the genetic architecture underlying disease risk.

**2. Biomarkers** (initially pilot studies to establish proof of principle of recruitment, follow up, data collection and practicality and reproducibility of laboratory techniques. These will be used as preliminary data for substantial follow-on funding applications)

(i) Longitudinal testing of patients’ plasma samples during carefully documented course/stages of disease for existing (e.g. suPAR27, TNF28, Hemopexin7), novel candidate (pVASP8, b3 integrin26) and future biomarkers, in blood and in cultured human podocytes exposed to disease plasma. The NURTuRE cohort is testing a panel of 20 biomarkers associated with chronic kidney disease, which can feed into this workstream if candidates of interest emerge.

(ii) DNA – whole exome/genome sequencing, initially targeted to those with steroid resistant and/or familial disease, with the aim to accurately stratify each local population.

(iii) Transcriptomics – microarray study on leucocyte derived RNA samples, aimed to define disease signatures correlating to disease activity29

(iv) Epigenomics – benefiting from expertise in the MRC IEU to analyse large scale methylation data30

**3. Description of IEU tools and their potential utility for analysing INS sample data:**

All of these studies will be underpinned by support from the MRC Integrative Epidemiology Unit (IEU) in Bristol. We have established collaborative links with Dr Tom Gaunt, Reader in Bioinformatics, to analyse the output from any genome sequencing and transcriptomic studies with his overall supervision. Of note he has a particular expertise in analysing epigenomics data.

The MRC Integrative Epidemiology Unit (IEU) has been instrumental in the development of methods that utilise genetic variants for causal analysis (Mendelian randomization)31. Novel developments include a database of genome-wide association study (GWAS) datasets and an analytical platform (MR-Base, *in preparation*) that support automated causal analysis of the relationship between traits and diseases. The samples described in this proposal offer the potential for future grant applications that will measure molecular biomarkers and evaluate their causal impact on disease outcomes. In addition, the IEU has been involved in the development of an analytical platform for genetic correlation (LD Hub, [http://ldsc.broadinstitute.org](http://ldsc.broadinstitute.org/), <http://dx.doi.org/10.1101/051094>) that offers the potential to dissect the molecular pathways underpinning phenotypes in INS, and potentially identify sub-phenotypes. For both these approaches it will be necessary to generate data on the relationship between genetic variants and INS phenotypes (using GWAS approaches) to generate datasets that can then be analysed with the wide array of public GWAS datasets curated in the MR-Base database.

These data will lead to **hypothesis driven applications** for clinical and biomarker based stratification studies, leading to mechanism based trials of novel biologics/compounds, as well as ‘personalised medicine’ based clinical trials of existing therapies to improve outcomes and limit toxicities.

**Long term benefits**

A key goal is sustainability beyond the initial set up, and benefits to LMICs include direct linkage to one of the world’s leading glomerular disease laboratories; establishing an affordable internationally connected registry; research focused local laboratory testing, and local sustainable expertise. The expertise learned will include data management; registry set up and data validation; epidemiological analysis of cohort data; bioinformatics analyses of biological datasets (e.g. sequencing data, transcriptomics); laboratory biomarker methodologies.

The Bagga group in Delhi are world leaders in conducting clinical trials in INS, demonstrating both the impressive numbers of children seen in a single centre, as well as dedication and expertise built up over a number of years (e.g. 16-24). They will therefore provide a core part of the group leading clinical trial design, training across centres and leading on relevant funding applications.

Benefits to the host nation include key collaborative links worldwide, and access to large cohorts of patients with rare disease and therefore the ability to adequately power studies, comprehensively test candidate biomarkers and apply mechanistic stratification according to the latest research.

Benefits to all include the ability to partner with industry for repurposing of existing novel drugs/compounds; commercial development of new biomarkers in a well tested clinical cohort; the power of a high quality biosample collection shared across centres and linked to detailed (anonymised) clinical data.

**Summary**

The long term vision is to have a collaborative and cohesive network of clinicians and core researchers in glomerular disease in childhood, who are able to identify and molecularly stratify patients, and conduct targeted clinical trials of novel and repurposed therapies, allowing access of the most relevant and cutting edge new technologies to developing country populations

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Impact - UN sustainable development goals

Communication Plan

The aim of the plan will be to: 1) deliver the required levels of increasing engagement to support work streams in individual LMIC centres; 2) to communicate activity and deliverables at various key stages; and 3) to promote the overall resource and outputs thereby encouraging further collaboration and achieving sustainability.

Communications activity in terms of key messages will focus on: 1) raising the levels of awareness and understanding of Stratified Medicine and patient cohorts in this area of renal medicine; 2) promoting the network and the planned benefits and impact; and 3) promoting any data/sample resource and emerging clinical networks to support future activity.

We have keen links to Kidney Research UK (KRUK), a facilitative organisation that is centrally involved in coordinating the current NURTuRE consortium. The charity has reach and influence over academia, multi-professional kidney care teams and people affected by kidney disease. KRUK has a track record of successfully developing networks to support project development, implementation and dissemination. Through the UK projects (RADAR and NURTuRE) the PI and team has built up expertise and capacity across the full range of communications activities needed to reach the required audiences -lay, general public(s), professional, parliamentary, industry and broader stakeholders such as other charities; BHF etc. This experience will be shared with LMICs

The charity provides the chair, secretariat and development support for clinical research activity under the auspices of the UK Kidney Research Consortium. This group is responsible for developing a broad portfolio of clinical study activity around the UK through a series of Clinical Research Groups and offers an excellent portal for effective spread communications.

The PI is an original Trustee of Nephrotic Syndrome Trust ([www.nstrust.co.uk](http://www.nstrust.co.uk)), an active UK charity with over 800 FaceBook patient members. This is used to continuously update the patient/parent community about research and cohort activities.

In addition to formal peer reviewed journals, the plan will involve a range of activities using traditional web and PR approaches as well as more targeted peer to peer and patient led engagement dynamics. Activity will also include advice to each centre on roadshows for lay audiences to increase overall project profile as engagement/participation in any clinical studies. Activity will also focus on supporting the PI and LMIC leads on presentations, posters and workshops/side meetings at selected professional meetings: Renal Association, IPNA, ASN, EDTNA etc. We will also submit articles including case studies into trade (industry), professional and patient web sites, member's newsletters and other publications.

We also recognise the importance of promoting activity and any future resource to industry and other key stakeholders and to achieve future inward investment to the UK to support the delivery of new innovation. We will do this through working with our current industry partners in NURTuRE as well as identifying new collaborators during the project stages and also working with the ABPI and MRC etc. We will organise an interim and end of project meeting to promote outputs achieved and to encourage further collaboration.