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| **PROTEA: Summary of the two reviewers’ comments**  Friday 24th March 2017  v0.4 |

Thank you for the opportunity to respond to the reviewers’ questions and comments. There are three main themes, and these deserve particular explanation before we address the others point-by-point.

1. The need for more detail about the research question and multi-disciplinary team methods that will be applied.

Our proposal focussed on developing a strong partnership and a sustainable infrastructure (human and IT). We did not want to pre-empt the work planned for months 1-6 (and subsequent James Lind Alliance work) to identify the priorities for kidney research in South Africa and so limited ourselves to quite high-level kidney-related research topics. These were set out in the section “Proposed programme of activities” and included:

* Analysis of South African Renal Registry (SARR) data to describe the epidemiology of treated end-stage kidney disease (ESKD) in South Africa (with later extension to Africa), with particular focus on evidence of inequalities.
* Analysis of existing cohort studies and routine healthcare databases to describe rates, healthcare costs and outcomes of diagnosed acute kidney injury (AKI), diagnosed chronic kidney disease (CKD) and untreated ESKD in South Africa.
* An economic evaluation using decision analysis to estimate the cost and cost-effectiveness of renal replacement therapy (RRT) in South Africa.
* Qualitative research will explore decision making and access to treatment, particularly for people from disadvantaged populations.
* Mixed-methods pilot work will explore the feasibility of developing an infrastructure for sentinel surveillance studies, efficient registry trials and cohorts linked to biobanks.

This programme represents a broad range of multidisciplinary skills, from clinical epidemiology and statistics, to health economics, qualitative research and clinical trials, all of which are included in the University of Bristol team. (Reviewer 2 was not clear how the proposal was multi-disciplinary.) In the proposal we cited similar work carried out in the UK by the University of Bristol and UK Renal Registry, as an illustration of what may prove possible in South Africa without pre-judging the outcomes of the discussions with key local stakeholders in months 1-6. (These examples are expanded slightly in response to reviewer 1’s question 1, below, with references.)

2. The need for more detail about the IT solution for the South African Renal Registry

While we have had a number of discussions with the SARR about their technological requirements, we feel that the most appropriate strategy at this stage is to avoid pre-empting those decisions. As set out in the section “Proposed programme of activities”, in months 1-6 we will send a team of registry IT experts to work with colleagues in South Africa to ensure that we fully understand the range of settings in which data will have to be collected before making recommendations about changes to data collection, options for data submission to the registry and the choice of database to hold the South African and African Renal Registries. (Some additional technical information is provided below.)

3. Uncertainty about the data that would be available at the SARR and a misunderstanding that research would be restricted to treatment for ESKD, i.e. dialysis and transplant.

Reviewer 2 has looked at the publically available SARR annual report and points out that only basic demographic data are presented, leading to the question whether any meaningful research is possible with the SARR data.

The SARR does collect longitudinal data – baseline data and annual follow up data. It also collects data on cause of death. Such follow up would, in Europe, enable them to be included in section A (individual patient data) of the ERA-EDTA Registry report and allow them to contribute data to many of the survival analyses undertaken by the ERA-EDTA Registry. The SARR has simply not had the statistical support to undertake these analyses until now.

This demonstrates that collection of the same very simple dataset in other African countries would allow similar treatment and outcome comparisons and collaborations as part of the African Renal Registry.

Further reassurance is provided by the collection of identifiable data which allows:

* Tracing of people against the national death register (as has been undertaken by one of the co-applicants, Prof Boule, for a cohort with HIV).
* Derivation of location of residence to allow studies of equity of access to treatment (as has been by the University of Bristol and UK Renal Registry teams in joint replacement and renal replacement registry data, respectively).

Finally, it is important to correct reviewer 2’s statement that “The proposed program limits itself to analysis of existing data in the SARR, which is already published in the SARR Report”.

* Our third objective is to “[analyse] existing cohort studies and routine healthcare databases to describe rates, healthcare costs and outcomes of diagnosed AKI, CKD and untreated ESKD in South Africa.”
* Our second 6 month delivery target is to “Review existing hospital and laboratory databases for AKI and CKD”.
* Our fourth and fifth aims are to “obtain permission and link routine healthcare datasets from Western Cape to study rates of diagnosed AKI and CKD in the community” and to “analyse routine data on AKI, CKD and ESKD to identify the most important inequalities in diagnosis, treatment and outcomes.”

We believe it is essential for this group to look at the earlier stages of kidney disease and available sources of data that might inform the planning of services to prevent or reduce harm from kidney disease and support research to improve outcomes for people (adults and children) with kidney disease in South Africa and wider Africa.

There are also a couple statements in the reviews which need a clear response:

Reviewer 2, comment 1 (R2C1). A perusal of the SARR reports indicates that it has only the most basic demographic data, and no longitudinal information. It is unclear what additional analyses will the investigators perform in addition to what is already reported in the SARR Reports.

This is not correct. Please see point 3 above.

R2C4. In terms of expansion of the research to other African countries, the ability of AFRAN/APNA to influence the local governments and healthcare systems is not established.

We do not entirely agree. There are several examples of where renal registry data has been used to influence policy, including Tunisia and South Africa. ([1](#_ENREF_1))

Tunisia: The Tunisian dialysis registry has had a major impact on the country's development of RRT since its establishment in 1990.([2](#_ENREF_2)) Registry data influenced decisions to increase the number of nephrologists, develop a new transplant programme, start new dialysis units and develop a kidney disease prevention programme. The rate of new patients starting RRT in Tunisia increased from 82 per million population (pmp) in 1992-1993 to 159 pmp in 2000-2001 and remains around this level.([3](#_ENREF_3)) Of note, the registry data was able to identify three regions reporting particularly low treatment rates in the elderly, which may have reflected regional obstacles to treatment.([2](#_ENREF_2))

South Africa: The first report of the newly established South African Renal Registry was published in 2014 (December 2012 data),([4](#_ENREF_4)) nearly 20 years after the previous SA Dialysis and Transplant Registry was last published (reporting 1994 data). Key findings were that the overall prevalence of RRT was 164 pmp, up from 70 pmp in 1994. This growth was largely due to an increase in private sector haemodialysis. The report revealed a markedly uneven distribution of RRT across provinces and large differences in RRT rates between the public and private healthcare sectors (73 vs. 620 pmp). The release of the report attracted prominent media coverage([5](#_ENREF_5)) and led to the national health minister, Dr Aaron Motsoaledi, convening a national summit on “*An effective approach to chronic kidney disease in South Africa*” in March 2015. It is hoped that a comprehensive approach and more resources will eventually flow from this initiative.

Partly as a result of these experiences, there is great interest around Africa in establishing the African Renal Registry, as has been demonstrated by the progress that has been made over the last 18 months. ([6](#_ENREF_6)) The importance of involving stakeholders, including health policy makers and politicians, was very much recognised in the proposal as an essential part of the work that will need to be done to ensure sustainability of the registry into the long term.

R2C5. Cohort studies and registry randomised trials would be based on the assumption that patients continue to receive long term RRT in large enough number for long enough - the data for which is not available.

We also do not agree with this comment. While access to dialysis is indeed restricted (as discussed below), there were 9,541 people on dialysis in South Africa at the end of 2014. Once on dialysis, people tend to remain on it long term – initial estimates of mortality on dialysis look comparable to the UK at around 10% per year. We think this indicates that there are more than sufficient numbers of people on treatment for ESKD to undertake cohort studies and registry trials in dialysis.

It is also worth repeating that this work will look at earlier stages of kidney disease, which affects many greater numbers – about 15% of the South African population are expected to have CKD ([7](#_ENREF_7)) and while rates of AKI are not known, they are likely to be at least the same as in the UK (approximately 5,000-10,0000 cases per million of the population per year).

We will now move on to address the other issues raised by the reviewers, which generally ask for more information about the proposed work.

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Specific questions (reviewer 1 only)

Reviewer 1, question 1 (R1Q1). Please provide additional details on the operational plan for development of the registry, including a risk registry, and on the research question and programme.

A. Operational plan and risk register

As explained above, the details of the operational plan for further developing the SARR will be established in months 1-6 during a visit by UKRR IT specialists to South Africa. During this, they will be able to find out more about the existing WinDev-based SARR database. Throughout the project we will encourage the SARR to adopt international coding standards where possible. We may find that this will require terms to be translated or new codes to be created for local conditions. We have experience of working with standards bodies.

We are aware that the infrastructure available in South Africa will vary considerably from location to location, with one member of the project (Mr Whitlock) having several years’ experience of implementing IT systems in Kenya. During months 1-6, UKRR IT specialists will also visit a number of settings in which data are collected and submitted to the SARR. These sites will be selected by SARR partners to demonstrate the range of challenges to data submission that exist so that the optimal solution can be found. The UKRR team has already discussed sharing knowledge with NIHR-funded researchers at the University of Cambridge who are using Open Data Kit to allow data to be collected through a number of interfaces such as mobile phones without the need for an active internet connection.

The UKRR has experience managing a Private Cloud that hosts over 40 virtual machines which support its work. In the past 2 years it has implemented a new web based system for the Renal Rare Disease Registry (RaDaR). This has been running now for a year and has been well received, with over 6,000 patients having been recruited using it. This was delivered on-time and at a much lower cost than comparable externally developed systems which gives us confidence that the same will happen here.

We hope this provides a little more detail about options being considered. Although a provisional project plan was included in the form of a Gantt Chart in the original application, a more detailed project plan (including a risk register) will be developed in months 1-6.

B. The research question and programme

The reason there was no single research question in the proposal has been explained above. It may be helpful, however, to see some examples of research that has been undertaken in the UK that we feel could be replicated (with modifications) in South Africa.

* Establishing the incidence of AKI (and 30-day mortality rates with AKI) in primary care and secondary care using routine laboratory data. See [www.thinkkidneys.nhs.uk/aki](http://www.thinkkidneys.nhs.uk/aki))
* Equity of access to RRT for people living in socially deprived areas (using registry data including location of residence). ([8-11](#_ENREF_8))
* Equity of access to the transplant waiting list, living donor transplantation and deceased donor transplantation for ethnic minority groups (using registry data including ethnic minority status). ([12](#_ENREF_12), [13](#_ENREF_13))
* Reducing late presentation with ESKD using an algorithm that runs in 30 biochemistry laboratories (covering 20 renal units) to identify people with rapidly declining kidney function and alert local care teams. ([14](#_ENREF_14))
* Reducing harm (death) from AKI using an e-alert, care bundle and education package - laboratory and hospital admission data from 5 hospitals and a stepped-wedge cluster randomised trial design. ([15](#_ENREF_15))
* Does vitamin D reduce all-cause mortality in dialysis patients – an individual patient-level randomised controlled trial ([www.journalslibrary.nihr.ac.uk/programmes/hta/1449127](http://www.journalslibrary.nihr.ac.uk/programmes/hta/1449127)).

R1Q2. On the registry, could you provide more information on how the work would link with the African Renal Registry and what can be learned from that experience?

The SARR has been asked to host the African Renal Registry, with data from participating African countries (Ghana, Zambia and Burundi) already being submitted to the SARR and held on its database as part of a pilot phase. These countries are largely using the SARR forms and processes for collecting and submitting data. ([6](#_ENREF_6)) Prof Davids chairs the ARR committee, with a co-chair from Morocco (Prof Jarraya). From a statistical and research perspective, we see Prof Davids and the expanded SARR team of local health services researchers becoming a methodological hub for the clinicians at these fledging national registries to go to for advice on registry methods and statistical analyses.

R1Q3. In terms of data collection and database creation and management, how will you ensure that appropriate technology (e.g., cloud, digital) will be employed to ensure that what is developed is appropriate, robust and frugal? What do you foresee as the main challenges in developing the database, collecting data and deriving insights? How will you address them?

See response to R1Q1 above.

R1Q4. Could you provide more detail on how the infrastructure that is being built will become self-sustainable?

The system currently used by the SARR is dependent on proprietary development software that is not well known (WinDev). This has meant that they have been reliant on a single individual for development and maintenance – a definite risk to the registry. As part of the project it is likely they will move to modern, supported Open Source technologies that have a wide pool of trained developers. The UKRR IT team will include South African staff in any development work that is undertaken so that they’re able to support the system themselves.

One option is for part of the system to be built using the software that runs the UKRR’s Renal Rare Disease Registry (<https://github.com/renalreg/radar>). This year we will be using the same software to build two additional systems: an International Renal Rare Disease Registry and a more generic Paediatric Rare Disease Registry. With the software being Open Source and more widely used, maintenance and development costs will be lower.

The other key part of sustainability is the development of a funding model for the registry and a plan to address this was included in the main proposal (see section “Sustainability plans”). The South African government has already demonstrated its support for the SARR by providing some component of their funding over the last 2 years and commencing work on regulations that will make data submission to the registry mandatory.

R1Q5. Could you better explain the long-term aspiration for research leveraging the registry?

In the long term we see the SARR providing a robust, efficient, multi-purpose data collection infrastructure which, supported by the expanded local health services research expertise, will deliver translational public health benefits that improve the experiences and outcomes of people with kidney disease in South Africa and wider Africa. In effect this means that SARR research will:

* Evaluate current practice variations (and their association with differences in outcomes)
* Inform service planning and investment (and monitor any resulting impact of investment on patient and population outcomes)
* Identify inequities in access to treatment (and target interventions to reduce these/ monitor the impact of interventions)
* Refine research hypotheses for interventional studies
* Generate evidence through efficient (registry) randomised trials that will change clinical practice through national and international guidelines and
* Monitor the adoption of guidelines and the ultimate population health benefits gained.

R1Q6. Will there be benefits from this research for the UK?

The programme has been designed to maximise benefits to the South African partners, but there will be many indirect benefits to researchers and research in the UK. There is a lot that researchers at all levels in the UK will learn from visiting and hosting their South African colleagues, including invaluable experience in health services research in the global setting. Closer working with colleagues at the International Society of Nephrology, US Registry and European Registry through the steering committee will strengthen links with other key players in global kidney research. In the setting of a registry that is evolving, it may be possible to innovate in a way that is more challenging when things are bigger and more established, with these innovations later adopted by the UK. Finally, the programme may generate natural history data or effectiveness evidence that is highly relevant to some minority populations in the UK, such as people of African descent and people with HIV.

R1Q6. Could you provide more information on your strategy for patient and public involvement, engagement and participation?

Two years ago, the UKRR established a Patient Council. This is chaired by a patient and has 10-15 patient members. This Council meets three times a year and is attended by the CEO of the Registry and the Medical Director. The patients hear reports on progress with national audit and plans for research and advise on patient facing information about the registry, such as posters and infographics explaining the registry to patients and plain English summaries of data from the annual report. They also steer UKRR strategy, for example prioritising the topic of work for our recently appointed nurse fellowship – the patient experience of dialysis access.

We feel this close working with patients has been has been highly beneficial for the UKRR, though of course the model may need adaptation for another society and culture. Mrs Fiona Loud, chair of the UKRR Patient Council, has agreed to be part of the PROTEA team and work with us to find the most appropriate way to involve patients and the public in the SARR.

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Comments (reviewers 1 and 2)

R1C1. The proposal would have benefited from a clearer articulation of the benefits for poorer patients, beyond the mention of a gap in treatment between rich and poor.

In high income countries, CKD and ESKD are more common in people with diabetes, hypertension, obesity, chronic infection and HIV, putting people from more socially disadvantaged areas at higher risk. Further, as AKI tends to follow acute diarrhoeal illness, trauma and surgery/ childbirth with complications, the same people will also be at higher short and long term risk from AKI. The extent of this in low- and middle-income countries still needs to be established, but it is highly likely that prevention programmes in this area will disproportionately benefit poorer patients, who can be left bankrupt when one family member develops kidney failure requiring dialysis.

R2C2. There is no information on the gap between demand for RRT and availability nor do the investigators provide a plan to address that.

R2C3. Analysis of only the available data would not allow explorations of issues related to equity and access to care, which will need to capture data on population that does not get RRT.

Our South African colleagues tell us that only 20-25% of people referred for consideration of RRT are accepted to receive RRT by the official panels. The qualitative researchers on the team feel that this may be an area to explore ethnographically, but there is undoubtedly also quantitative work that could be done to capture the harm that is being experienced by patients and the currently unmet need of the population. Some further detail on how we will deal with this in epidemiological terms has been covered in the responses above.

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