WG3: Minutes of Position Paper Working group (lead: Nick Selby)
13.10.2017

Participants:
Nick Selby; Maarten Taal; Jarle Rorvik; Paul Hockings; Eli Elkefjord; Nuria Garcia-Fernandez; Stephen Marticorena-Garcia; Alberto Ortiz; Enrica Gintou; Valerie Said-Conti; Janka Slatinska; Isky Gordon

Summary of discussion points:

1. Agreed that the document would be structured around the following headings:

- Diagnosis and classification of disease (Aim: 'to use MRI to identify or measure an aspect or aspects of biology that are relevant to CKD')
- Patient stratification (Aim: 'to use MRI to predict important outcomes in patients with CKD')
- Informing choice of treatment, monitoring response to treatment and/or toxicity (Aim: 'to understand the clinical implications of renal MRI images').

Other suggestions that have been put forward by email include: the need to have reference value for MRI biomarkers as a valuable aim; to be explicit on what study design(s) we have in mind; to consider interplay between imaging biomarkers and other novel biomarkers (e.g. plasma/urine); to include a discussion of the role of MRI in personalised medicine; in the 'choice of treatment' chapter consider phase I-II trials of new promising drugs that include fMRI, on the one hand to study acute hemodynamic effects of the drug as well as short term changes (detect potentially nephrotoxic or nephron-protective drugs before any other biomarker); the link between kidney diseases and cardiac disease.

2. To follow discussion of the key clinical questions, the position paper will also include a section on 'strategy' or 'the way forward'

3. There was a discussion of different MRI measures to be used in clinical studies. Agreed that a pragmatic approach for multicentre studies would be to define a core set of MR measures that all centres can deliver, but at the same time important not to limit expertise in more advanced techniques that exists in different centres. Study design would allow centres to have flexibility to add additional measures depending on local capability – ideally this would be supported by networks that can then collaborate regarding standardisation/QC of the 'non-core' techniques (between centres with similar interests). There was some discussion regarding DCE, not used by all centres; in those with experience not using in patients with GFR<45ml/min.

4. Specific points about the design of potential clinical studies that were discussed:
    - To study biological validity of MRI, cross-sectional studies with comparison against percutaneous renal biopsy were considered important. However renal biopsy has a number of limitations as discussed. The options that were discussed to address this included: animal models to provide an alternative platform for validation; to look at nephrectomy specimens; and to validate against clinical outcomes as an alternative but complimentary strategy.
    - Validation of MRI against clinical outcomes was also considered crucial. Although this is a separate question to establishment of biological validity, in practical terms it would be beneficial and more efficient to link the study of both: a cross-sectional study with baseline comparisons but then with longitudinal follow up with assessment of clinical outcomes.
    - For longitudinal studies, the group agreed that it was important to assess 'hard' clinical endpoints: this means that we will need to design a study that will have sufficient numbers/power and duration of follow up to establish risk of ESKD/doubling serum creatinine. Agreed that there was significant risk in terms of testing MRI against surrogate endpoints (i.e. want to avoid establishing a surrogate of a surrogate) but surrogate endpoints (e.g. CKD progression, eGFR trajectory) could be included as secondary endpoints.
    - To keep studies feasible, sample size (at least for initial studies) could be kept smaller by studying high risk populations. The discussion concluded that initial studies may start with more advanced CKD (e.g. CKD 3B/4 so higher events, easier to recruit from nephrology, more pronounced histology), although in the longer term the study of earlier CKD will also be important, and this may be particularly interesting to pharma. Pharma may have more CKD 3 interest as there is a perception that there may be more reversibility at that stage. The point was made that stabilisation of CKD would also be a benefit.
    - Discussion around measures of renal function to be included in studies. Many of the current comparisons in published literature are MRI measures against estimated GFR, which has some strengths but also weaknesses that means it is not always a gold standard comparator. Discussed the alternative of measured GFR, although this requires multiple timed blood sampling (e.g. for iohexol clearance for example) that may reduce patient acceptability. The latter may also be limited by different regulatory rules in different countries, and that some centres may not have experience/capability. Conclusion of this discussion was that there may be different requirements in different types of study. Measured GFR would be optimal for cross

sectional studies, however for longitudinal studies looking at *change* in renal function eGFR would be better. Other suggestions – include cystatin C that may help improve accuracy of eGFR equations; and if measured GFR is too burdensome/costly to measure in all subjects could measure in a subgroup

- Aetiology: needs to be considered in patient selection for studies. A number of different groups were discussed: different aetiologies of CKD; AKI on CKD; transplant patients per se; transplant patients with ATN or acute rejection; important to include paediatric populations. Discussed that it would be possible to design a study that would include separate cohorts with pre-specified proportions, although this does have the risk of making the results harder to interpret. Agreed that to be robust, power calculations would need to show adequate sample size for primary endpoint in each of the separate cohorts; in turn this would mean a relatively small number of subgroups. How best to decide clinical groups? Pilot studies would be really useful and these may already be in progress across the PARENCHIMA network.
- Efficient study design with registry outcomes was also suggested as a potentially useful model for tracking endpoints such as dialysis initiation.

5. Agreed to include the role of MRI in assessment of suitability, response or toxicity to treatments. Agreed that conceptually it would be possible to add MRI onto planned studies; this would be far easier that doing a fresh study from the beginning. It would however need to be agreed by the sponsor and CI and this would need time, effort and funding. Planned SGLT2i studies were discussed as one example of this. As well as new treatments, it would also be possible to plan this for existing treatments e.g. for specific renal disease in which patients are being treated with immunosuppression, or for drugs (new or existing) that are used in transplantation. A further option would the the study of patients who undergo protocol biopsies post renal transplant, as in some of these the biopsy leads to a change in treatment that could be assessed with repeat MRI.

6. Agreed that the paper should mention in brief a discussion about how to operationalise MRI for multicentre studies but that this section should be kept brief.

Agreed actions

1. Circulate a plan for the manuscript by end of October (lead: Nick Selby). This will include specific sections of the manuscript with word counts (total word count ~3000)
2. Group to return comments by 14th November
3. Volunteers for writing contributions to the manuscript by 14th November

4. 1st draft of manuscript 6th January 2018