PARENCHIMA Launch Meeting: Work Group 3
Bergamo
2017.7.13-14

Participants:
Anna Caroli; Anita Harteveld; Jaap Joles; Iosif Mendichovsky; Cyril Moers; Carlos Nicolau; Agogho Odudu; Aaron Oliver-Taylor (Gold Standard Phantoms); Doug Pendse; Andrea Remuzzi; Nick Selby; Paul Summers; Stravros Tsantis; Jean-Paul Vallee; Marcos Wolf; Paolo Brambilla; Antonio Barletta, Giuseppe Remuzzi

Meeting slides to accompany these notes

Meeting notes:
- Welcome from Anna, introductions

PARENCHIMA overview from Anna
- Key points: bottom up networking to build and expand research activities.
- Networking costs covered, research costs are not covered
- Aim is to establish funded EU wide research studies
- Oversight from Management Committee
- PARENCHIMA: led by Steven Sourbron
- Overall aim is to eliminate the main barriers to multicentre MRI research studies and to employ MRI biomarkers in CKD by improving reproducibility and standardisation, develop and open-access toolbox for software and data, demonstrate biological and clinical validity.
- 5 groups
    - WG1 reproducibility and standardisation
    - WG2 research and development tool box
    - WG3 multicentre clinical trials
    - WG4 training programmes
    - WG5 dissemination and exploitation
- Duration: 4 yrs

- Aim of WG3 in more detail
    - Validate MRI biomarkers against histology or reference methods
    - Determine clinical utility – prognosis of CKD or whether longitudinal changes or progression can be demonstrated
    - Initial proposal was for large cross-sectional study (in biopsied CKD patients) followed by longitudinal follow ups
    - 1st year – should be devoted to developing funding applications
    - 2nd year – pilot studies and set up infrastructure
    - years 3-4 – larger clinical studies that will continue beyond the life of the COST action
    - Currently 45 people involved in WG3, ethos is inclusivity so if others are interested they will be welcomed
    - Requirement to stick to COST objectives at the outset but can modify the work plan as the project evolves

- Will start from what's available
    - E.g. repository for SOPs, protocols, patient information sheet, accreditation docs, template docs
    - Collect data about expertise and centres
    - Develop multicentre studies and turn these into funding applications

- Review of table of current studies (Excel sheet as previously circulated)
- Table divides up into disease areas: ADPKD, CKD, Diabetes, hypertension, AKI and some others.

- <u>Marcos updated on launch meetings from other WGs</u>
    - WG1: first action is a survey: platforms, manufacturers, licenses etc. Also aim to produce a white paper – aimed at common ground, simple. Split MRI techniques up into different task forces
    - WG4: Innovative training network (branded as 'renalis') identifying innovative training programmes, focus on integration. Deadline for ITN application January. Renal experts with multidisciplinary exposure – commercial linkage attractive to EU funders. Request for feedback/learning from previous submissions.

Meeting objective 1: Strategies for data sharing and documentation sharing

- Agreed that plans for retrospective data merging for previous studies is not feasible – too much heterogeneity. Suggestion would be to also organise the table into similar imaging modalities – this may help assess feasibility
- New approach in Switzerland to encourage open access of data during grant applications, similar in other countries. To consider this in forward planning.
- Creating a repository of study documentation was discussed as a more feasible action
    - General agreement that this was a good idea
    - Want to avoid ending up with a large amount of separate files; so for each document uploaded it should be accompanied by a short synopsis. Alternative is to use a 'Wiki' – this was discussed but concerns re practicality of this.
    - List of useful docs:
        - Study protocols; patient information sheets; letters to GPs, main ethics application form, SOPs for image acquisition and data processing; quality controls, documents pertaining to other studies; non-imaging biomarkers that are collected alongside MRI data, advertising materials for patients/HCWs
        - Discussed language: to upload docs in their original language without translation
    - Didn't yet discuss what the accompanying synopsis should contain
    - Agreed that there were two elements to this – firstly collecting the documents, and secondly starting to identify commonalities, key themes for standardisation as we move forwards. Agreed to focus on the first of these actions initially.

Meeting objective 2: Available MRI data and clinical study documentation based around the Excel table of current studies across participating centres

Which MRI sequences and clinical areas of interest: please see the summary slides from each centre for the background to this point.

Discussed how it would be possible to define a core set of sequences that most centres could deliver, and then newer or more innovative techniques could still be included in a large multicentre study in those centres with capability i.e. sub-study for the 'non-core' modalities.

Proposal of core sequences: anatomical imaging (optimised protocol for cortico-medullary differentiation and volumetry), quantitative T1, T2 and T2* (BOLD), diffusion weighted imaging (DWI), renal artery flow (phase contrast). These could then be applied to large populations.

Alternative approach – we assume that WG1-2 will solve technical issues, so we plan studies based on ideal MRI parameters. Several studies in different disease areas could then be planned, choosing MRI sequences that are most appropriate to the clinical question. This approach may allow for linking of centres with capabilities to do particular studies that could then be pulled together.

Techniques that may be harder to standarise/operationalize across many different centres include: ASL, elastography, DCE, oxygen 17-MRI. These could still be included in large studies in those centres with capabilities as described above.

In the UK, a survey was performed by the UKRIN about detailed assessment of capabilities of different centres - this could be rolled out to European centres.

We also discussed the cross-platform issues, and that we could group centres into vendor specific groups to address some of the reproducibility issues.

Discussed the different approaches – HVs, patients with disease who are being scanned anyway, and diseased patients who are not going to be scanned. Most CKD patients (unless that have CKD) will fall into the latter group.

Contrast enhanced MRI – discussion. Most centres agree that gadolinium based contrast for research purposes in CKD is not being used at the present.

Meeting objective 3: Novel initiatives

Which clinical areas?

Start point of discussions – presentation by Beppe Remuzzi. All three studies are using renal MRI as endpoints. These studies have not yet started; flexibility still exists in terms of defining MRI measures that will be included. Some members will propose these to clinical colleagues to ask about other centres collaborating as recruiting centres.

- Study 1: prospective RCT with long term (36M) extension of renal morphological effects in 42 patients with sympathetic denervation (early versus late) in refractory hypertension.
- Study 2: Tolvaptan versus Tolvaptan-Octreotide in ADPKD; short term cross over with extension to 36M. n=42. GFR>30ml/min, age 40-60.
- Study 3: RCT of acovopan (CCX168, Novartis, C5A inhibitor) versus placebo in C3 glomerulopathy. 26 weeks treatment with 26-week extension period. Serial renal biopsies (x3). n=44. Opportunity for comparison between MRI and renal biopsies over time.

Diabetes, in clinical practice patients not often biopsied.
iBEAT-DKD; potentially definitive study already planned and funded.

What are the important clinical questions?

Important clinical questions are predicting clinical progression/clinical outcomes. Our over-arching aims are summarised as:

1. Improved staging of CKD (better than eGFR and albuminuria) as per points 2 and 3
2. Differential diagnosis/differentiating differential pathologies
3. Prognostication: predicting risk of CKD progression, risk of ESKD
4. Predicting response to therapy, measuring response to therapy. To include novel and existing agents. At an individual level (personalised medicine)

Discussed how eGFR is not a gold standard against which to compare MRI measures.
Suggestion not to forget the validation step. Validation studies could be planned to complement existing larger studies e.g. iBEAT-DKD
Also:
As a strategy to plan initial studies: select clinical group(s) (clinical stratification); reproducibility of MRI measures in disease patients (test-retest); comparison of MRI measures against gold standard. At present, although there are some potential caveats (particularly around sampling error), renal biopsy is the best standard against which to compare. Ensure that patients are well characterised, including measured GFR in preference to eGFR *(please note that this doesn't give split function – NM studies would be required for this).* This would appear to be an important early step and approach endorsed by the group. Also note that the reproducibility work can be done separately or together.

Certain studies can be planned for patients undergoing biopsies. These include: allograft nephropathy, CKD who are biopsied as part of routine care, Study 3 above. These are selected groups, but can be starting point and will fit the above strategic approach. MRI studies of live donor transplant patients are also a group that may provide specific insights.

To consider guidelines around biomarker development processes in other areas e.g. Roadmap for imaging biomarkers in cancer. Nature Reviews Clinical Oncology 2016. doi: 10.1038/nrclinconc.2016.162.
http://www.nature.com/nrclinonc/journal/vaop/ncurrent/full/nrclinonc.2016.162.html
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm268555.pdf
http://www.cancerresearchuk.org/sites/default/files/imaging_biomarker_roadmap_for_cancer_studies.pdf
https://images.nature.com/full/nature-assets/nrclinonc/journal/vaop/ncurrent/extref/nrclinonc.2016.162-s9.pdf

We currently don't have normal ranges for healthy volunteers; this also needs to be planned, so include HV control groups in the planned studies. This could also be an early objective. Consider this to be done across different vendors and across different field strengths (including 1.5T)
Round robin phantom for the different measures – this would appear to be the remit of WG1

Technical validation should not prevent moving forwards with clinical studies and validation.

Is there an opportunity to work with pharma companies to measure treatment effect?

Agreed that further discussion around important clinical questions is still required (see below)

Meeting objective 4: Proposed review articles from WG3

- Agreed that we should plan a systematic review to rigorously report currently published normal and abnormal ranges of different MRI measures. Divide into the different measures for the review (one review per measure, maybe start with BOLD, then DWI, qT1). Describe the approach of populating tables with MRI methodology, clinical conditions and HVs in which it has been used, and the range/distribution of measures reported. Ultimately, this will have relevance to WGs 1-3 and there may be potential for collaborative work. Start with the skeleton of the review – define the headings and subheadings/structure of the tables first. Once these are agreed, then the work to populate these can begin. The review should be clinical and should be published in nephrology (not imaging) journal e.g. KI
- Discussed consensus paper to define the important clinical questions that need to be addressed with MRI. To include broad base of clinicians, senior experts in CKD, expert histopathologist(s). To follow up feasibility and potential funding of this outside of the meeting, and then plan the best way forward.
- Possibility of survey between the groups that are members of WG3 to address simple practical questions that may lead to guidelines. Ask specific questions e.g. contrast use – no data around these practical questions in the literature. Could add to technical and processing survey templates.

Distribution of tasks

Leads for systematic review topics were agreed:
DWI – Jean Paul Vallee
BOLD – *to ask* Menno Pruijm
qT1, qT2 – Marcos Wolf
ASL – Ags Odudu

The leads will

- Identify contributors to the systematic review
- Agree standardised approach/template so that the individual reviews are of similar format. Table format similar etc. Standard title e.g. MRI biomarkers: …*add name of measure..* Circulate this with whole WG3 and ask for comments within a set deadline. First template to be drafted by Iosef, Anna and Nick and circulated to Jean Paul, Menno, Marcos and Ags
- Agree authorship at the beginning of the process. Guidelines for this were agreed: Authors should be those who actively participated to the review or actively/substantially reviewed the manuscript, but not to automatically include the whole of WG3. This will be decided by the senior author (lead for the systematic review as above). All manuscripts to include Anna Caroli to reflect her contributions via leadership/co-ordination.
- General introduction for series to be written based on minutes from today (Anna Caroli)
- Previous white paper on imaging biomarkers was structured around well accepted steps: proof of concept, standardisation, qualification and validation, outcome. Use this as the framework for each review.

- The approach will not be a formal systemic review with statistical combination of the individual study results – the aim is to usefully present all of the current papers in the area in one place.
- Clinical scope defined to include: HVs, all forms of diffuse acute and chronic parenchymal disease and renal transplantation; studies of renal cancer to be excluded. This scope may need to be revisited and can be subsequently redefined by the groups working on the systematic reviews.

- General structure:
    - technical table (acquisition; sequences; orientation; resolution; matrix size; TE; TR; flip angle; acceleration factor; modality specific details e.g. b-values for diffusion etc., pharmacological manipulation),
    - post-processing table
    - clinical table (disease category, patient description, outcomes (histology, GFR etc), detail of how the MRI measures are reported e.g. both kidneys combined, therapeutic intervention, results in terms of range and distribution of the particular MRI measure)
- Include 'not reported' within a large, inclusive table
- Patient preparation (e.g. hydration protocols etc) out of scope

Ask wider group as to whether include DCE as an additional topic

Dates for actions
First draft template circulated to leads of reviews: end of July
First draft of manuscripts: Berlin meeting October 2017

Consensus paper
Discussed whether or not this would be preceded by a consensus meeting. Funding for this not currently clear. Aim is to define and publicise the clinical need. This could be planned as a dissemination activity (and so would fall within WG5 budget).
Could approach the chief nephrologist from participating centres.
Alternative approach would be with a survey – this could reach a wider population.
Include patient views/input.
Nick to work up an options appraisal for this. Liaison with Steven and Anna.

Other topics of discussion: Funding opportunities
Brief discussion at the end of the meeting. Some suggestions e.g. ERA-EDTA, Horizon 2020 but not enough time to complete this discussion. Will also be discussed across the WGs and the whole COST action.