Minutes WG3 Meeting
Utrecht 23rd April 2018

Attendees: as per agenda

Meeting started with a tribute to Jarle Rorvik, given by Steven Sourbron. All recognised how Jarle's work has contributed to the advancement of renal MRI and specifically to the COST action, and agreed that the NDT supplement should be dedicated to his memory, following his sudden and untimely death.

Agenda:

- Anna gave an overview of WG3, and outlined purpose of today. Next steps for WG3 are to plan future multicentre/multinational clinical studies. Specific aims of the meeting as follows:
    - To agree a co-ordinated funding strategy to attract the necessary funding to support clinical studies. To explore the follow themes in parallel:
        - Add MRI to existing studies
        - Large scale multinational grants
        - Collaborative studies ('modular' approach) with national level funding with linking and sharing of data collected in the same way between centres that adopt similar protocols
    - To consider how to 'lobby' for specific grant calls/funding opportunities
    - To start planning clinical studies and grant applications in alignment with the above strategy
    - Aim to identify current concrete opportunities
    - Define clinical area(s) in which to start
    - Agree ways of working to allow multiple applications to be developed at the same time
    - Position paper will provide a framework for discussions today

- SESSION 1: Adding renal MRI to ongoing renal initiatives
    - German CKD study
        - 5000 CKD patients (CKD 3 or albuminuria, under care of nephrology, nine recruiting centres)
        - Broad range of aetiologies, including 50% of cohort in which diagnosis is unknown, 30% diabetes. Discussion that 'diabetes' as the most predominant cause of CKD covers a range of pathophysiological changes
        - 10 year follow up
        - Biosamples stored for future analysis
        - As per October 2017, 5217 enrolled: 1.5% lost to follow up, 0.04% withdrawn, 5.1% left study, 10.9% mortality. Just about to complete 5 year follow up visits
        - Currently no renal imaging
        - Could look at cross-sectional renal MRI in substudy: would have retrospective clinical course, and there is still several years of outcome follow up for prospective outcomes. Could potentially select out those who have had renal biopsy.
        - Alternative proposal: integrate renal MRI into clinical care (AKI/CKD prior to biopsy, healthy donors prior to nephrectomy, patients with specific aetiologies of CKD)
        - Funding from a variety of sources: initially public grant funding, then private foundation, more recently industry funding
    - NURTuRE
        - National UK CKD prospective cohort study in UK
        - Currently still recruiting, some features in common with German CKD study
        - Particular focus on biomarkers with a centralised analysis of renal biopsy
        - Target sample size 3000, to be recruited within 12M across 12 centres, ethics approval to follow for 15years

        - Using a central database at the UK Renal Registry; this link to UKRR will help with outcome tracking (e.g. mortality, ESKD), also will link to other national databases (HES, ONS)
        - Kidney Research UK providing a supporting role in set-up and governance, but didn't provide funding
        - Funding initial came from industry, initial engagement and negotiation facilitated by KRUK
        - Industry funding in return for access to some samples
        - Also obtained MRC funding, after project set up and core funding was already secured.
        - MRI not currently included
        - Opportunities: add MRI as a substudy to NURTuRE or initiate a new cohort using similar study design and infrastructure. For the former, timing unlikely to make it for baseline visits (within next 8M) but more feasible to consider coinciding with year 1 follow up visits (18M time)
    - CKD-REIN and CKD-DOPPS
        - CKD cohort study connected to French renal registry
        - 3600 patients, within this that patients constitute the French cohort of CKD-DOPPS. 50% CKD 3, 50% CKD 4
        - 5 year follow up planned, study due to end 2020
        - Biosamples collected at baseline, 2yrs, 4yrs
        - Includes data collection on practice patterns, particularly focussed on transition of CKD to RRT, conservative care etc.
        - Crosses public and private sectors
        - Includes PROMS as well as clinical outcomes
        - No imaging currently involved
        - Funding comes from public and industry funding – total budget €11million
        - Differences in different regions of France discussed e.g. incidence of diabetes as predominant cause of ESKD is very different between NE and SW regions
    - General discussion about the three cohort studies
        - Not sure if studying patients after progression answers the question as to whether MRI predicts progression; for this ideally a prospective approach will be more valuable
        - However, value may come from describing the MRI changes that happen with progression
        - Menno – in his dataset, correlations were strongest with future prediction rather than what has happened before, but this was just with BOLD (100 CKD, 60 hypertension, 40 HVs)
    - UK Renal Imaging Network
        - UKRIN structure and aims presented
        - MRC infrastructure grant described, aims of standardisation
        - How this will link to PARENCHIMA discussed – should be complementary, and that progress on a regional/national level may be quicker and then can be shared.
        - Discussion as to whether other PARENCHIMA countries could form imaging networks
    - EIBALL (European Imaging Biomarkers Alliance)
        - Subcommittee of European Society of Radiology (reports to research committee)
        - Running for 5yrs
        - Working on a mission statement: to facilitate biomarkers development, standardisation and to promote their use in research and clinical practice through collaboration. This applies to multiple organ systems, but aims are the same as PARENCHIMA that is just focussed on the kidney.

        - Are also working on a roadmap that will be discussed at the next committee. Three elements within this: establishment of functional biomarkers, working with groups to standardise biomarkers, then an educational arm
        - Aims to avoid silos of people working on biomarkers in isolation
        - Network approach across Europe but also to link to equivalent group in the US
        - Gave the example of how performance of phantoms can differ, which is a block to biomarker progress, and this type of issue can be dealt with via networking to ensure everyone is on the same page
        - EIBALL does not offer support directly; EIBIR (based in Vienna) have a strong office and do offer support but this has to be commissioned/funded (but they are not for profit) to help obtain European funding. May also be able to help with horizon scanning/advising about appropriate grants. Individual institutions have to pay a fee (€1000 per year) to be EIBIR member, PARENCHIMA can't be one of these.
    - BEAt-DKD
        - IMI-2 collaboration and funding; 50% EU funding, 50% industrial partners (support in kind)
        - Focussed on diabetic kidney disease
        - One work package of 6 is on imaging biomarkers
            - Developing a new prospective cohort to look at this
            - Running one new study 'iBEAT', 5 different recruiting sites that will each recruit 100 patients
            - Initial FU is 3yrs, aiming to extend this to 15yrs
            - All sites will supply the same MRI data that will be aggregated centrally in an imaging biobank
            - Each study arm has its own aims: e.g. histology, microvascular imaging, PET, progression, novel MRI biomarkers
            - As such, not set up as a multicentre study, but set up as a 'modular' collaborative study, each centre writes own protocol, gets own ethics etc
            - This will provide quite extensive protocols for quantitative MR on Phillips and Siemens 3T
            - This model may be applicable for PARENCHIMA
            - Funding for iBEAT is about €4million
        - Aim is to get whatever biomarkers come out of the project on the way to regulatory adoption

- SESSION 2: Potential funding sources
    - Dutch Kidney Foundation
        - 2016: total income €21 million; 62% spent on research innovation
        - Mix between competitive grants and DKF initiated projects
        - Competitive grants: innovation, translation, talent
        - DKF strategy: societal aims (patient driven) and economic aims (engage government policy) are both considered. Want to align with that National Science policy of the Netherlands
        - Many countries don't have renal specific charitable funders (outside of KRUK and DKF), this came out of discussion of joint funding that may cross-national barriers
    - EU calls
        - Horizon 2020, discussed calls 2019-2020, and gave an overview of the programme
        - Horizon 2020: Excellent science; Industrial technologies, societal challenges. Different calls require multicentre approach or not.
        - Within societal challenges, one theme: health demographic change and well-being – this is where most of the clinical studies are funded within Horizon 2020

        - Also – an opportunity for training exchanges: Maria Sklodowska Curie actions, and ITN fellowships
        - In current call, only one that may be relevant – Call: Better Health and Care, economic growth and sustainable systems. Very broad with lots of subtopics
        - 2019 confirmed, but still some doubt about topics for 2020. For 2020, there may be an opportunity to interact with programme contacts to try and influence content of call
        - 2019: 6 calls presented; 4 were research and innovation actions. Deadlines for next round are October 2018
        - Broad list of clinical studies that they fund, including medical devices and companion diagnostics
        - Source to have a look at this: participant portal, http://ec.europa.eu/research/participants/portal
        - At present, UK participants are still eligible and can request budget, at present this holds true until UK leaves EU. Following this, still aiming for a collaborative approach with co-funding approaches
        - Caterina requested position papers etc to be sent so she can circulate to other national Horizon 2020 contacts
    - National calls – Swiss case
        - In Switzerland, there was a specific grant call for COST action holders and only applied to the first year.
        - This is to help salary and research costs to help acquire data within the COST action
        - Submission: renal diffusion MRI in CKD: a multicentre approach (Geneva and Fribourg and Bern). 300 patients, MRI within 24hrs of renal biopsy. Recruit over 4 years. Aiming to use MRI to predict 40% fibrosis on renal biopsy. Protocol will include DWI, T1 and T2, but may be able to expand to protocol
        - Awarded €250k; works out at €800 per patient. Mainly on MRI scan time, data analysis and research nurse time
        - Only other country that has a similar programme is Czech republic
    - Kidney Research UK (KRUK)
        - Two parts of the process: direct funding; facilitation of obtaining funding from other areas including industry
        - Strategy aligned to a UK Renal Research Strategy; has been useful in discussions with other funders. Includes a specific recommendation to maximise cross-disciplinary research
        - UK Kidney Research Consortium provides a structure for 14 different sub-speciality research groups (Clinical Study Groups), also a regenerative medicine network and a fibrosis network.
        - Discussed KRUK's role in set up and funding negotiations of NURTuRE, same model has also been used for other studes e.g. PIVITOL study of IV iron dosing in haemodialysis patients
        - KRUK also facilitated a joint approach between Phillips, GE and Siemens that came together to support an MRC grant application. Agreements weren't for financial support but for support in kind with technical support etc.
    - ERA-EDTA
        - Not a funding agency – has given grants previously but this wasn't a recurrent activity
        - Other activities that may be relevant to PARENCHIMA
            - Annual conference with 8000-9000 attendees, Journals
            - Working groups in sub-speciality areas, Eur Journal Best Practice initiatives
            - Registry
            - Young Nephrologist's platform

        - Environmentally friendly approach discussed as an ERA theme for a long term commitment
        - Discussed the possibility of creating an Imaging Working Group. This would require submission of a plan to the council. This would attract €20k per annum for meetings etc.
    - NIDDK
        - July 12-13th 2018, NIDDK is hosting a meeting to review state of the art in renal imaging, there will be a presentation on PARENCHIMA.
        - Includes techniques, biomarker qualification, industry panel that includes newer techniques
        - Links to talks from outside of the field to give clinical link
        - Then there will be plenary and break out sessions 'where are we going'
        - Anna will represent PARENCHIMA and will explore links and how to join networks
        - This will be an open meeting so interested parties can attend
        - Cationised ferritin to visualise glomeruli and Ultrasound based elastography
    - ESMRMB (European Society for Magnetic Resonance in Medicine & Biology) – didn't present

SESSION 3: the way to go with biomarkers

- FDA biomarker regulation
    - Made the case for new biomarkers to identify CKD progression over a shorter period of time
    - There are different pathways for BM approval: diagnostic tools versus in drug development. In the latter, this can be drug specific or more general. This is key to decide this at outset as different stakeholders will be involved in the two processes, the technical validation requirements will also differ.
    - EMA and FDA processes are similar but not identical and of course completely separate processes
    - Need to be clear about how biomarker will be used (Context of Use, COU) before engaging with regulators, and requirements will be different e.g. for use in Phase II versus Phase III trials
    - Recent update in process follows a change in US law
    - Early engagement starts with a feasibility meeting with multiple stakeholders: NKF, FDA (several branches), Critical path director, PARENCHIMA
    - Process and timelines are set out for both FDA and EMA
    - It is a drawn out process that requires resource
    - Lots of experience within Regulatory departments of large pharmaceutical firms
    - Discussion that biomarker can be qualified but this doesn't necessarily specify the 'assay' (e.g. the technique to measure the biomarker). However the technical validation aspects of the biomarker will be needed for qualification.
- TKV in ADPKD
    - TKV clearly associated with speed of progression
    - First described in 1981, followed by a number of studies (generally using ultrasound)
    - Larger, ultrasound studies early 2000s showing the same thing
    - Led to the formulation of CRISP who aimed to use MRI to track TKV and link to progression
    - CRISP started with 4 centres who followed a standardisation protocol, phantoms and travelling kidney (4 patients)
    - Initial studies showed that MRI was highly accurate for measuring TKV
    - 2007: process for qualification started, with a joint statement from PKD foundation and FDA
    - 2012: evidence to show value as prognostic biomarker and was being used as an endpoint for TEMPO 3/4 clinical trial (Tolvaptan)
    - TKV biomarker adoption applied for on the basis as a prognostic biomarker in 2012, final submission went in 2013.
    - FDA approved as a prognostic biomarker 2016

AFTERNOON SESSION

- Plenary discussion
    - Disease area – general agreement that it's too early to be prescriptive about this, in reality studies in different areas will be complementary rather than competitive
    - Radiology view – quantitative data important, but don't forget about the image side of things. Point made that use of an imaging biomarker early in the disease course may generate normal looking images and at this stage it's the quantitative data that may be important
    - Proposal for one idea for an initial clinical trial:
        - EU funded
        - Use centres with MRI expertise
        - Focus on general CKD but to exclude of ADPKD
        - Cohort trial: scan at baseline then follow up clinical outcomes
        - Subgroup of patients with biopsy but not essential in all
        - Consider cardiac imaging at the same time; may need to benefit from cardiology input
    - Agreement for the above study idea in following discussions – with specific advice to look at Horizon 2020 application to map out a timeline for a large, well-funded comprehensive trial, and in the meantime consider what other activities can be performed to strengthen the application: testing protocols, pilot data, sharing expertise between centres. This should also include the standardisation aspects of MRI measures that will be used which will need to be in place prior to a multicentre trial running. Disseminate outputs from UKRIN when these become ready for wider sharing.
    - Cross-validation of other biomarkers from existing cohorts may be something to consider
    - Unknown diagnosis group discussed – at present we don't know how the outcomes for this group differs from other CKD aetiologies, and also what MRI would tell you in these
    - Single nephron GFR measured by MRI would also be extremely interesting with several clinical applications

- GROUP DISCUSSIONS
    - Large EU grant: agreed this was a good way forward.
        - Lobbying – agreed this was a good idea but didn't know ways to approach this. EIBIR, European Kidney Health Alliance both mentioned but neither ideal.
    - Working group at ERA/EDTA – agreed this was a good idea, and maybe would be one way to secure sustainability for meetings to continue after the end of COST funding
    - Minimum requirements for sites – depends on outputs from WP1, but there are also elements to this that are additional to MR technical details, and WP3 could work these up
    - Website: could register new studies as they come along to help with sharing of protocols, patient selection etc. that would help align studies from different centres that want to develop plans to combine prospective data
    - Previously agreed that the responsibility for standardisation of MRI measures lies with WP1

- ACTIONS AGREED AT END OF MEETING

Action	**Person(s) responsible**	**Due date**
Review Horizon 2020 calls for the next two years and identify those that may be potentially suitable	Anna/Nick to draft email asking for senior WP3 members to do this	
After identifying suitable call, map out timeline between now and submission		
Identify a senior figure to lead Horizon 2020 application, along	Anna/Nick to draft email to	

with a small team of others who can contribute to grant writing, and a wider team who would be part of delivery of grant. The latter should include a statistician so that power calculations can be considered early in grant writing process. The lead person should probably not be from the UK. This should also have a wider membership that WP3 only.	all WP3 members asking for EoI for: lead person, people willing to contribute to grant development, check that institutions can handle EU grant	
Investigate ways of 'lobbying' to support /Horizon 2020 grant application	Jean Paul Vallee to find out details of how this was done on a previous grant he was involved in	
Identify a WP3 member to draw up minimum standards for sites to participate in multicentre trials (but without specifying technical details of MRI sequences at present); this can be shared with WP1 to add the technical details afterwards	Anna/Nick to draft email asking for WP3 member to lead on this and liaise with WP1	
To move forwards with plans to add renal MRI studies to existing German, French and UK CKD cohort studies	Maarten Taal, Kai-Uwe Eckhart and Christian Coombe to look at viability wrt to their data and meet at EDTA to discuss next steps	
Work up application to ERA for renal imaging to be adopted as a working group	Anna/Nick to draft email asking for WP3 member to lead on this	
Propose a session on renal imaging for future ERA/EDTA conferences	Peter Blankestijn	
Send position paper to Caterina (Italian national point of contact for Horizon 2020)	Anna	