Minutes of the MATURA Patient Advisory Group (MPAG) – Seventh meeting

Room: Room G.06 Joseph Rotblat Building, Charterhouse Square

Date and Time: Wednesday 2nd July 2018 2pm-4pm

Attendees:
Zoe Ide (ZI), MPAG Chair
Dr Frances Humby (FH), Consultant Rheumatologist, Barts
Caroline Wallis, Lay member of MPAG
Hannah Maltby (HM), Lay member of MPAG
Sonia Jeevanason (SJ), Lay member of MPAG
Phoenix Hoare (PH) Lay member of MPAG
Charlotte Austin (CA), Research Involvement Officer, Arthritis Research UK
Myles Lewis (ML), Consultant Rheumatologist, Barts
Felice Rivellese (FR), Clinical Fellow, QMUL
Gaye Hadfield (GH) MATURA Project Manager WorkStream 1, QMUL
Laura White (LW) EMR Clinical Trials Centre Manager, QMUL
Jo Peel (JP) STRAP Clinical Trial Manager, QMUL
Isabelle Garvey (IG) Study Coordinator, QMUL
Ali Fahmi, Computer Science, QMUL
Hamit Soyel, Computer Science, QMUL
Paul Corzen, Computer Science, QMUL

Apologies:
Professor Costantino Pitzalis, MATURA Lead
Professor Anne Barton, MATURA Co-Lead
Simon Stones, Lay member of MPAG
Lesley Cooke, Lay member of MPAG

1. Welcome:

Zoe welcomed everyone to the seventh MATURA Patient Advisory Group (MPAG) meeting and thanked them for attending. Apologies were noted. There were no comments on the minutes of the previous meeting.

2. MATURA Updates

2.1. General

An ongoing action is for lay summaries of all publications to be made available on the MATURA website.
Action: GH to follow-up

The summary of all the materials available for patients is now REC approved and copies have been printed (A5) and distributed to all STRAP sites.

The patient-patient video will be covered by Felice (see below)

The 6-monthly MRC review was on the 16th November MATURA and additional funding to open STRAP sites in EU was approved.

An event was held on the 15th December 2016 to mark Kellgren at 10 years in Manchester.

On the 6th February 2018 the annual Scientific Symposium was held in Manchester, there were updates from the many research groups contributing to MATURA and Zoe presented on MPAG's progress.

At the end of February, a second article was submitted to NRAS for publication in the Spring edition of their magazine. The article reviews the changing landscape of diagnostics for RA from past to present and what the future may hold if stratification of treatment becomes a reality.

2.2. Upcoming events:

The next MRC review is 3rd May.

On the 1st of June 2018 there will be a 2nd CiTi/QMUL "meet the researcher" patient event, this time there will be informal talks, laboratory visits and a MATURA stand for researchers to meet patients, with afternoon tea.

MATURA will be hosting a stand at the Barts/QMUL Science Festival on the 20th June 2018 this annual event is to stimulate children's interest in science and medicine. Sonia asked if the incidence of RA is increasing in children, the general view is that is not the case but the awareness in increasing. Charlotte noted that there had been an increased awareness at Arthritis Research UK since the merger with Arthritis Care which runs a dedicated section for families. She also reminded the group of the excellent facility for adolescents hosted by UCL they have 170 young people who participate in PPI activities.

2.3 STRAP

Jo Peel (STRAP trial manager) updated the group:

To date 131 patients have been recruited, the target is 207, with 20 UK hospitals open and recruiting patients.

Up to end of April:

- 1630 study visits have been completed with a very high patient adherence 98%-100%.
- 114 patients have reached primary endpoint (the 16-week visit)
- Numbers of synovial samples analysed and in storage are:
    - Baseline: 131
    - Week 16: 40
- 908 blood samples have been processed and stored
- 523 Ultrasound assessments performed

The recruitment breakdown by sites shows Barts to be the top recruiter, there are a number of sites that haven't recruited for some months and they are being contacted to determine the reasons for this and offered help where appropriate.

Three sites have opened since last MPAG: Cannock Chase, New Cross and Salford, 1 site is temporarily closed (Salisbury)and a final UK site is in set up (Edinburgh)

EU-Sites in set up include:

- **Belgium**- Louvain- recruited well to another EMR trial
- **Italy**- 2 sites in Milan, Novara and Cagliari
- **Spain**- Barcelona
- **Portugal**- Lisbon

These hospitals all recruited well to R4RA, also a biopsy driven trial.

The Wolverhampton trust opened recently and is recruiting well.

Recruitment is below target and we are supporting sites where we can e.g. fellows from Barts are travelling to perform biopsies where resources are an issue.

The MRC will be asked to write to sites emphasising the importance of recruiting.

Zoe asked what materials are provided when a site opens, Jo advised that she provides materials at the site initiation visit and the study monitors check on stocks when they do their 6-monthly visits to sites.

Caroline is due to visit MRI and will see what materials are on display in the clinic and feedback at the next meeting.

Sonia asked if the patients get feedback on their test results. Jo explained that in order to ensure there is no bias in the data this information is not made available to the clinical teams who must remain 'blinded' until the results of the study are analysed. The patients' details are not available to the coordinating team trial team so the information would need to be provided at the end of the study by the clinical team. **Action: GH to raise at the Trial Management Meeting**

2.4 Funding applications

2.4.1 NIHR Fellowship Application

Felice Rivellese is a research fellow and is applying for an NIHR transitional fellowship, title: **Synovial B cells inform treatment response in Rheumatoid Arthritis (SyBRA)**

Transitional fellowships support researchers to move from laboratory research to clinical research.

He previously analysed synovial tissue for the presence of Mast cells and showed that they are linked to progressive disease. The fellowship would allow him to gain expertise in performing synovial biopsies.

The aims of the research are:

1. Validate B-cell count by comparing methods
2. Compare B-cell counts during the stages of the disease
3. Understand if the presence of B cells predict response to B cell depleting medicines

The most important aspect is the training, acquiring the tools to become an independent clinical researcher. Felice proposes to do this in the following ways

1) Ultrasound - *EULAR courses on US and local training*

2) Ultrasound-guided synovial biopsies - *supervised-training and transition to independency*

3) Epidemiology & Statistics - *Course in Manchester*

4) Bioinformatics - *Local training and interaction with bioinformaticians*

Felice went on to discuss PPI involvement, he is keen to ensure that the patients' needs are addressed in this research. He proposed that more detailed information about the synovial biopsy procedure would be helpful for the clinician to use with the patients. He noted that a video has already been developed and proposed that putting the questions and answers from the video in a leaflet so that those who prefer to read the information have this option available. The questions for a second video where a patient talks to a patient who has undergone a biopsy have REC approval and Felice would be happy to progress this as part of his fellowship.

He asked about additional tools and what format would be best (online or printed), he suggested information leaflets including testimonials from patients.

He will also be involved in organising a webinar on synovial histopathology with EMEUNET (association of young rheumatologists and researchers within EULAR) and this will allow dissemination at EU level which is important for STRAP.

Zoe asked for clarification on where input was required, Felice would like input from MPAG to prepare a leaflet to describe synovial biopsy and for his PPI activities to be integrated with the group.

Sonia offered to be involved in the second video as she has had a biopsy.

Action: Felice to send lay summary to MPAG members

Zoe would like to see the training programme a clinician has undergone outlined in the patient leaflet on biopsies as this is an important aspect for patients.

Action: **Felice to consider including this information**

2.4.2 **NIHR Funding opportunity "Mechanisms of Health Interventions"**

The application to analyse R4RA samples was reviewed here at the last meeting, thank you for your support and feedback, unfortunately it was not funded by NIHR on this occasion and we re-submitted this application to Bart's Charity on 4th April 2018.

2.4.3 MRC Experimental Medicine Challenge Grant

We are submitting an outline grant to the MRC the deadline for outline applications is 31st May 2018. Proposals to this call need to involve an experimental challenge in humans.

Building on our stratified medicine programme this funding would allow MATURA to move to a second phase.

The process in our current studies (STRAP & R4RA) is:

- Define patient pathotype (cellular)
- Then randomize to treatment to ensure equal numbers in each pathotype (pathotype is not linked to treatment)
- To answer the question pathotype associated with treatment response?

We are proposing a further study (STRAP- 2) where the process would be:

- Use transcriptomics (what genes are active in the synovial tissue) data from PEAC to define groups likely to respond to treatments
- Identify the prevalent transcriptomic signature in a small group of patients (to stratify patients)
- Treat with this group of patients with the biologic predicted to work best for patient
- To answer the question: Can we stratify patients by signature?

We will hear in August/September whether or not we have been invited to submit a full application.

2.5 Development of a DAS App – Dr Fran Humby

Fran explained that the treatments for RA involve immunomodulatory drugs, medications that control the immune system driving the inflammation. These drugs range from low cost to very expensive injectable biologics. If not treated well the effects on patients can be severe with increased morbidity and mortality plus large costs to the NHS & society

One of the objective measures used to monitor treatment is the Disease Activity Score (DAS) this is a composite measure made up of

- The number of swollen joints
- The number of tender joints
- CRP/ESR measures in the blood
- A visual analogue score from the patient of the overall disease activity in the last week

Patient outcomes are better when low DAS scores are achieved through treatment but the challenge is the variability in DAS scores that is not picked up by biannual clinic visits. A visit can coincide with either a peak or trough of disease activity and so can lead to either over or under treatment which can have serious consequences of either side effects from over treatment, or joint damage from under treatment. The ideal scenario would be to see the patient more frequently but this is not possible in the current outpatient model that is driven by capacity rather than need, a factor not limited to just NHS but many other healthcare models worldwide.

One of the biggest challenges in maintaining tight control is the management of patients on biologic drugs, these are expensive injectable medications which are a treatment not a cure so are long term medications that can often be started in a patients' 40s and continue for decades. These are expensive and although rheumatology is one of the smallest specialties it consumes a quarter of the drug budget (with only oncology spending more).

There are risks associated with Biologics e.g. increases in shingles, TB, and some types of skin cancer.

Tapering biologic drugs can be effective in 30-40% of patients and can be achieved by reducing the dose or increasing the interval between injections. This can lead to significant health economic benefits by reducing side-effects and costs but there are risks associated with tapering e.g. flare of RA or secondary failure of biologic

One way to circumvent this is by remote monitoring of disease activity so that it is more frequent and not just done at clinic appointments. The QMUL team are developing an app dedicated to remote monitoring of patients on biologic drugs- this project has funding via the Barts Charity and the Project is called the 'BioT-app'.

DAS apps have been developed by other groups (e.g. NRAS, UoM) but they are not interactive.

It is known that patients are almost as accurate as clinicians in measuring tender and swollen joint counts but current DAS-apps are not widely used and barriers to their uptake include that they are: isolated from the NHS IT systems so information is not fed back to the health care team; no joint count training available; Apps are not interactive.

A prototype BioT-app is now available, patients enter their DAS scores which are sent to the clinician for review and the patient receives a message on the results. This has been shared with patients and it is now undergoing the first 4-week pilot phase before entering into a 12-month clinical study which will evaluate its effect on patient outcomes. This 12-month study will also provide real life prospective data for the computer science team to develop the Bayesian network methodology.

One patient meeting has been held and feedback included

- Breaks down barriers to access information
- Reduction in medications
- Involved in care
- Integrated with NHS system
- Wider remit for RA care not just biologics
- To set-up some intelligence in the app

The vision is to create an app with intelligence and to also apply it to clinical trials, this would reduce the inter and intra observer variability and would increase the frequency of the assessments without an increase in costs. Data from both the BioT-app and established patient cohorts (MRC-funded PEAC study) will provide data sets for machine learning and development of the artificial intelligence prototypes.

Members confirmed that with appropriate training they would be keen to use such an app. Zoe noted that there may be opportunities to capture more precise information e.g. for a patient with one large swollen joint who may have an overall low DAS score a single joint could be monitored.

Fran asked about receiving messages, Phoenix thought feedback would be very helpful particularly as it could give rapid feedback on blood tests. He has been using the app 'Rheumabuddy' which tracks pain, stiffness and mood rather than DAS but it is completely patient led. Fran asked how frequently Phoenix used the app he said his use had tailed off, he also uses an app to interact with his GP practice, for ordering prescriptions and booking appointments, he suggested that integrating all the systems would be helpful and for example a patient could then be alerted when they need a blood test.

Funding for the BioT-App has been based on the potential cost savings on biologics but Fran is very aware that for patients it is very frustrating not to get test results in a timely fashion and that even repeat prescriptions do not always run smoothly.

Phoenix felt that providing results would allow patients to feel more involved and they would then be encouraged to get blood tests done. Prompts from the system to do this would mean that clinician time could be saved which then frees up more time for those patients who need to be seen.

Charlotte pointed out the analogies with other chronic diseases e.g. diabetes and the potential to learn from other areas. The BioT-app is one of two case-studies and the other is diabetes.

Need to ensure the system:

- Is appropriate for different levels of education;
- available in different languages;
- allows a way of contacting anyone who doesn't log on for sometime

For example, the app could allow the patient to select the language and the appropriate level

Paul asked what it would take for patients trust the algorithm to give them feedback and advice e.g. prompt for blood tests. It was clarified that the test results would then be reviewed by a clinician who would always have oversight of the process and the ability to intervene if needed.

The view was that if the automated system allowed drug tapering, and for patients to be seen when needed, then the benefits are likely to outweigh any potential risks.

The effectiveness of the system will be subject to a research study so data will be available for patients to scrutinise before any implementation plans are put in place.

Caroline highlighted that humans as well as machines can make errors, for example at her annual appointment the clinical staff had advised her that no changes were necessary but when her drug

supplies arrived she had been swapped to a biosimilar, information she felt should have been given at her appointment.

Sonia logs aspects of her health in her diary and asked if this could be captured in the app? At present the app captures the DAS score but could be extended to other characteristics in the future.

2.6 What can we learn from gene expression in RA? – Myles Lewis

Myles introduced himself - a Rheumatology Consultant responsible for data analysis for MATURA, he noted that we now have the ability to measure vast numbers of factors, this leads to large volumes of data that need managing and analyzing.

Our DNA doesn't generally change and can be considered to be a personal recipe book, DNA generates mRNA and this leads to the production of proteins. The human genome has 10 billion base pairs of DNA much of which is constant so we concentrate on looking at the parts that change which are known as 'genetic variants', the latest technology measures 1m base-pairs. These variants are single nucleotide polymorphisms (SNPs) are like single letter changes in a book of 10 billion letters. For RA we are often looking at about 100 SNPs so a very small number of the total genome.

RNA can be measured more easily; we measure about 50m reads at a time. Unlike DNA, RNA can be changed so one gene can code for more than one protein, so measuring the proteins is the most difficult problem.

The biggest problem is scale of the data and we have access to a system called eMedLab to store the data.

We often refer to the analysis of 'omics', the gene is genomics, RNA is known as transcriptomics, proteins – proteomics. We have been developing tools primarily for scientists, there's now lots of data that is publicly available but to access to it requires programming skills. Myles is often asked by researchers who have an interest in a particular gene, what that gene shows in the PEAC samples, as a result he has built a website to do this that doesn't require programming skills. He demonstrated this by typing the name of a gene in the website, this generated a large amount of data on the gene e.g the level of the gene in the 3 main synovial pathotypes (lymphoid, myeloid and fibroid) and relation to clinical presentation e.g DAS score. We can use this to see which genes actually matter in RA. There is information on 20,000 genes in this system and a funnel plot is used to show, in a picture, the relation between the genes and other characteristics.

For about a third of the genes we don't know what they do but for the genes we do know about we can group them together in modules, so instead of looking at lots of individual genes we can look at a smaller number of groups of genes or modules. So instead of 20,000 markers we look at 200 modules. An example is the interferon group of genes in blood and we can see that in some RA patients interferon is increased (interferon is produced in response to viruses). The move is to get data more interactive and accessible.

Phoenix asked about the sample sizes and the data. Myles explained that the data he has shown is transcriptome data from 150 patients with RA and that Manchester have done more genetic studies. Manchester have looked at which genes increase the risk of RA but this doesn't measure the environmental factors. These studies require huge numbers of patients and controls, the latest GWAS (genome-wide association study) used data from 70, 000 patients and 130,000 controls and found 120

genes of which 60 were already known, of the new ones the function of about one third is unknown. This type of study is very expensive study.

Zoe asked if it is possible to look at what environmental factors trigger RA. Myles said there is a lot of focus on triggers e.g. specific bacteria in the gums but it's very difficult to differentiate an association from a cause, sometimes animal models can help resolve these questions.

In STRAP we are finding out if biopsies will help to decide which treatment is best and we have seen there are lots of measurements that can be made on the biopsies, determining which are the important ones will be more difficult.

2.7 Arthritis Research UK new website "Involving People with Arthritis" – Charlotte Austin

Charlotte explained that Arthritis Research UK have developed a new section of their website through collaboration with patients. One request was for a "news and activity" section which includes patients' stories on involvement, Charlotte asked if anyone would like to write about MPAG and their involvement in the project.

Sonia offered to do this for MPAG. **Action: Sonia to send her article to Charlotte**

ARUK can also post any involvement events on this page and it should be used as a resource by MPAG.

2.8 The next MPAG meeting will be held 2-4pm (refreshments from 1.30pm) on Wednesday 17th October 2018 at Charterhouse Square, QMUL (meeting room to be confirmed).