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

Room: Large Endocrinology room (D119), Charterhouse Square, QMUL, London

Date and Time: Monday 13th November 2017 2pm-4pm

Attendees:
Zoe Ide (ZI), MPAG Chair
Professor Costantino Pitzalis, MATURA Lead
Professor Ann Morgan (AM), Consultant Rheumatologist, Leeds (joined by V/C)
Dr Frances Humby (FH), Consultant Rheumatologist, Barts
Caroline Vass (CV), Research Fellow, WorkStream 2 (joined by V/C)
Elizabeth Hensor (EH), Medical Statistician, WorkStream 2, Leeds (joined by V/C)
Caroline Wallis, Lay member of MPAG
Simon Stones, Lay member of MPAG (joined by V/C)
Hannah Maltby (HM), Lay member of MPAG
Sonia Jeevanason (SJ), Lay member of MPAG
Lesley Cooke (LC), Lay member of MPAG
Charlotte Austin (CA), Research Involvement Officer, Arthritis Research UK (joined by V/C)
Deborah Maskell (DM), MATURA Project Manager WorkStream 2
Gaye Hadfield (GH) MATURA Project Manager WorkStream 1
Laura White, EMR Clinical Trials Centre Manager
Jo Peel STRAP Clinical Trial Manager

Apologies:
Eleanor Goddard (EG), Lay member of MPAG
Professor Anne Barton, MATURA Co-Lead
Cameron Neil, Lay member of MPAG

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1. **Welcome:**

   Zoe welcomed everyone to the sixth 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 MATURA Discrete Choice Experiment: Caroline Vass

DCE: Caroline Vass joined meeting via videolink

Caroline is a Health Economist researcher at University of Manchester, she is interested in peoples' preferences for a new stratified medicine approach to treatment of RA and how they value different health care goods and services. Previous comments received from MPAG on the survey were very much appreciated.

Slides accompany these minutes.

Caroline wanted to find out that if we had a prescribing algorithm (biologic calculator), how good would it have to be for people to want to use it for their treatment decisions over current conventional methods of prescribing.

Developed Discrete Choice Experiment survey, supported by economic theories to explain how/why people make choices, which can then be analysed to understand demand and what drives that demand.

Pilot study on 100 healthy volunteers complete (4 of which had RA). The survey was administered online and comprised of background information, training materials, choice sets (hypothetical healthcare options) in this case picking a healthcare option based on:

1. Delay to start of treatment.
2. Ability to predict who would respond.
3. Ability to predict who would not respond.
4. Risk of serious infection, resulting in being hospitalised.
5. Cost saving to the NHS.

These attributes were traded off then people asked to decide based on this.

Results: 100 people (not RA, but to understand if the survey would work). Feedback was requested and most said it was interesting, easy and they were interested, a couple said it was too long.

Then some statistical analysis was done:

1. People prefer the good things e.g. correctly predicting the right treatment
2. People preferred the biologic calculator over conventional methods, i.e. personalised medicine (significant).
3. People liked the cost saving to the NHS (significant).
4. People disliked negative attributes, like a delay in starting treatment, risk of infection.

Further analysis was done on how people weighed up different attributes and how much people were willing to trade different attributes off – tables in slides.

Final survey is planned in November, link being sent to Rheumatology Clinicians, RA patients and more members of the public (about 900 people). These will then be compared between groups.

Please contact Caroline on caroline.vass@manchester.ac.uk with any questions.

Comments:

- This survey was tested extensively prior to release to ensure people had all the information and objectives before they took part. This was pilot only and they acknowledge that RA patients views might be very different.
- This survey is hypothetical only, it is explained to participants that this is in development, and while the hope is to translate it to the clinical field, it currently is not 100% correct in predicting responses.
- Size of group - 100 people, each making 6 choices, so 600 observations. No demographic information used at this stage. Disease experience is more relevant in the next stage of the survey rather than demographic information like gender.
- Final sample size will be 150 clinicians, 150 people with RA, 150 members of the public. Also, 150 further people who might receive a different version of the survey (without the background info) to validate the survey, as Caroline hypothesises that people will need the background information to understand the survey correctly. There will also be some Psoriasis patients as well.

Future support from MPAG: Caroline would like to return in 2018 with results proper for feedback and as there may be things she can't explain that the group might be able to enlighten her on.

2.2 MATURA work stream 2 DNA genetic work: Nisha Nair

Nisha is a researcher working in Manchester and gave an overview of the work going on in Manchester, following on from the update Professor Anne Barton gave last year and led on to her epigenetic work as well.

Slides accompany these minutes.

Aims of work stream 2:

1. Identify predictors of response (genetic, gene expression and DNA methylation).
2. Measuring treatment response – changes in DAS28, inflammation markers and swollen joint counts and whether they correlate with the genetic findings.
3. Using existing and newly generated data from RA studies around the UK.

Identifying small alterations in the genome called SNPs in people with RA and those without. We are looking at 1000s of SNPs and we need to find out if these SNPs can be used to predict treatment response.

Samples: 1,800 anti TNF samples, 1,000 Methotrexate samples and 800 rituximab samples. All data put on TranSMART platform that Mike Barnes showed the group last time. Analysis is ongoing.

Methotrexate: there is an association between SNP and change in DAS28 score. MTX pathways may be involved in signalling between cells that could be affected by these SNPs.

Anti TNF: associations with changes in DAS and its separate components, for example, swollen joint counts. 16 genetic SNP associations and 13 of these were strong (FTO gene in swollen joint counts) further work planned.

Epigenetic analysis: Epigenetic patterns are changes to the structure of DNA, but not the genetic sequence itself, this can affect whether a gene is turned on or off. Affected heavily by environmental factors like smoking and diet.

DNA methylation is an example of epigenetic modification, the more methylation occurring means the less expression and vice versa.
Nisha is looking at whether DNA methylation has an influence on the way patients respond to Methotrexate. She had 36 excellent responders to MTX and 36 non responders. Samples were taken at baseline and 4 weeks to see if there were any differences in DNA methylation.
Results: initially found 12 genetic regions that showed differences, out of these 12, 5 regions were replicated in new samples. Two regions associated with lower swollen joint counts and 3 regions associated with lower levels of the inflammation marker, CRP. Analysis ongoing.
Plan is to combine this new epigenetic data with the other genetic and SNP data that we already have on these patients, to see if it relates throughout.

There are other new analytical techniques being developed within MATURA to analyse all the different genetic data together and creating novel statistical models of analysis.

Future: Currently combining all the data available to find correlations, to make the analysis more robust. This is where MATURA is so good, that Nisha has access to so many variables and so many different types of data to reinforce whatever is found along with the expertise of other analysts in collaboration that will help.

ACTION: DM to re-circulate Nisha's lay summary of the review paper.

2.3 Reweighted DAS28 score – validation of a new disease activity score for RA: Elizabeth Hensor via videolink (apologies for sound technical problems).

This work was a collaborative effort across the MATURA group.

Disease activity score includes tender and swollen joint counts, C-reactive protein and a patient visual analogue scale (VAS). It was developed before the widespread use and ultrasound, so the aim here was to explore whether a new DAS, re-weighted against ultrasound detected joint inflammation would be a better score to use in studies looking at biologic predictors of response to treatment.

Note: this is not to replace the current scoring system in the clinical setting, this is to look at to whether it would be better to re-weight the DAS when looking at large studies looking at predictors of response to treatment.

Historically, joint examination and blood tests of inflammation and patient reported outcomes. Joint exams (especially tender) made the greatest contributions to distinguishing between high and low activity, when it was assumed that starting a new drug or stopping one for lack of effect indicated high disease activity, and stopping a drug due to remission or staying on the same drug for a long time indicated low disease activity. They wanted to re-visit this, but instead of using treatment decision as the outcome, they had an actual measure of the joint inflammation, detected using ultrasound. These were compared in 3 datasets to see if there was an association.

It found that swollen joint count and C-reactive protein were both associated with inflammation of the

joints. Also, once these two scores were known, the other two (tender joint count and patient VAS) didn't contribute any further inflammation information. They concluded that they could drop these two measurements and re-weight the first two and combine them to make a new disease activity score, which they went on to test in a completely new cohort. They used x-ray damage measures and whether joints were damaged or erosions were present. The new DAS proved better at measuring inflammation and damage/erosion score.

Summary: Tender joint and Patient VAS scores are not associated with the ultrasound detected joint inflammation or x-ray detected joint damage.

The new revised DAS score based only on swollen joint count and C-Reactive protein shows stronger association with x-ray joint damage and they believe this new DAS measure will help identify predictors of treatment response. It won't be used as it is in the clinical management of RA as they wouldn't want to omit the patient experience of the condition.

It could help find biologic predictors of response, therefore in the future it could help identify new pathways by which we could personalise a patients treatment according to their genetic profile.

Future: Paper submitted to Annals of Rheumatic Diseases, but it is under review.
DM requested a lay summary, once paper is published.

2.4 MATURA update

In May 2017 the MRC approved a no-cost extension of STRAP. Patient recruitment to continue to November 2018, with an end date for MATURA of 2nd March 2020. This extension included a re-profiling of the budget for 5 WS1 partners to move to per-patient fee model.

WS2 was subsequently extended to 2020 to allow for joint WS1 and WS2 analyses.

On the 21st June 2017 we ran a Rheumatology stand at QMUL/Barts Science Festival. School children could have their hands examined by ultrasound and try on gloves that mimic the effect of having arthritis (we have been invited to next years' event on 20th June 2018)

Despite terrible weather a 'Meet the researcher/BBQ' held at QMUL in July 2017 was enjoyed by both patients and researchers. We will look to use this as a model for future events.

Elin contacted all the STRAP sites in August 2017 to offer support for PPI contacted re PPI. She had responses from Cardiff, Leeds & Newcastle

A MATURA Project Steering Group was held on the 18th of September 2017 and STRAP recruitment was discussed (see below for details), an expansion of the study to a selected number of EU sites was approved by the group.

2.5 The STRAP clinical study

GH introduced Jo Peel who is the trial manager for STRAP and R4RA. The study is based on synovial biopsy and 111 patients have been randomised to date. The target is 207 by November 2018. We have 17 hospitals recruiting and the rate of recruitment vary across sites.

Two new sites have opened Kings and Royal Free, and there are a further 3 in set-up: Wolverhampton Trust (hospitals at Cannock Chase and New Cross, PI Dr Sabrina Raizada) , Salford (PI Dr Hector Chinnoy) and Western General in Edinburgh (PI Dr Neil McKay).

Salisbury is temporarily closed due to a shortage of resources to deliver the study.

Recruitment strategy includes:

- Opening more hospitals
    - Hospitals who cannot do the biopsies can partner with hospitals that can
- Encouraging patient engagement with research
- Facilitating recruitment with videos of patient interviews
- Amending the protocol - a proposal to reduce the number of study visits to increase patient participation was considered but there were only a small number of visits that could be dropped without affecting the study aims and this was not thought to be a sufficient number to increase patient participation.

We achieved the recruitment target agreed with the MRC up to August 2017 (5 per month) but recruitment has dropped in last 3 months (Sept-Nov 17). We had predicted that recruitment would increase to 7 or 8 patients per month when new sites opened but this has not been the case.

ZI asked if the reason for the drop in recruitment was due to sites that had previously recruited well not performing. GH confirmed that this was one of the contributing factors.

PH asked about the criteria for patients joining the trial and whether these are particularly strict. GH explained that the criteria are standard for patients moving onto biologic treatment, in addition patients need to be willing to have a biopsy and able to commit to the monthly study visits. It was noted that competition from trials that target the same patient cohort is an issue, particularly as there are an increasing number of commercial studies (of biosimilars) which provide high financial reimbursement and are high priority for the NIHR Clinical Research Network. Patients are not paid to participate in the trials but receive out of pocket expenses e.g. for additional travel.

The expertise to deliver the biopsy is one of the main barriers to opening more sites and until clinical utility of the procedure is confirmed through research studies the NHS will not invest in providing this resource. As new sites require training and some time to gain the expertise ZI stressed the importance of ensuring that we get maximum returns from those that are already in a position to deliver the study. CP advised that the goal is to have all UK hospitals able to do the synovial biopsies and that this can be done by rheumatologists or interventional radiologists; in order to capitalize on centres that have the expertise we will be looking to open sites outside of the UK that have recruited well to biopsy trials.

Three sites in Europe (Louvain in Belgium, Lisbon in Portugal and Novara in Italy) have contributed over 40 patients to the biopsy driven trial R4RA and JP is working to open STRAP at these sites early

in 2018. Whilst there is a significant amount of work involved in opening these sites we believe this will be worthwhile.

UK sites were all contacted in October to remind them we need them to continue to deliver in addition to the EU sites.

One of the clinicians requested that we produce a summary sheet describing all the materials we have available to support patient participation in the STRAP trial. This has been prepared and is with the Research Ethics Committee (REC) for review. We are planning to make an additional video of a patient talking to a patient about the biopsy process and the questions that will be asked in this video have also been submitted the REC:

Why do they need me, what help could I be?

Will it hurt?

How long does the biopsy take?

Will it help me?

What's in it for me?

Would you do it again?

We continue to produce any materials to support STRAP and have asked all the lead clinicians to feedback on what they would find helpful.

We talked at the last meeting about the advantages for patients of being involved in clinical trials, the lead research nurse at Whipps Cross has produced the following summary:

- Treatments when no other options available in the NHS
- Early access to novel new treatments (5+ yrs. before launch)
- Flexible appointment times around patient availability
- Frequent long appointments enabling education of patients about self-management
- Continuity of care by same member of staff
- Opportunity to meet other patients with the same condition and share knowledge
- Seen promptly

2.5 NIHR Funding opportunity "Mechanisms of Health Interventions"

A grant application is being submitted to NIHR to support further analyses on the samples, GH presented an overview and asked for feedback form the group.

R4RA very similar to STRAP but it is a different patient cohort, these are patients who have been treated with an anti-TNF but this has been ineffective. R4RA is evaluating whether we can predict which of the two biologics, tocilizumab (TOCI) or rituximab (RTX), would be best.

Synovial tissue is collected, the number of B-cells determined and patients are randomized to TOCI or RTX. The R4RA study is funded by NIHR, 161 patients have been recruited to date and recruitment ends December 2017. The study is evaluating whether the number B cells in the synovium can be used to predict response to RTX, method we use in R4RA (& STRAP) to determine the number of B cells is to stain the tissue, examine under a microscope and manually count the B cells.

ZI asked if the study had reached its target, GH explained that the aim was to recruit sufficient patients to achieve 80-90% power in the analyses and 161 will give over 80% power.

NIHR is the research arm of the NHS and funding for this money is restricted to research meeting the following criteria:

1. The use of samples collected using NIHR funding
2. Evaluation of known mechanisms of action in the samples
3. Methods to improve stratification

Not about discovering new markers, there must already be some evidence of how treatments/stratification works. The samples that have previously been collected are used to provide further evidence.

It is known that Rituximab reduces B cells (mechanism of action)

Will look at cells in the synovium and molecules in the synovium and peripheral blood

Cellular

Digital Image Analysis (DIA), in this method a sample of the synovium stained for B-cells will be scanned by a computer and the proportion of B-cells of the total area is calculated.

This is being proposed to improve the histopathology method. We want to see if there is a more reproducible method for stratifying patients by B-cell number (so the method is not influenced by how experienced the person counting cells under the microscope and can more easily be implemented in labs throughout the country). Our aim is to move towards a fully automated process.

Molecular

Gene signatures. Eighteen genes were identified in an earlier pilot R4RA study that were associated with high levels of B cells in the synovium. Looking for expression of these genes in the synovium may provide a better method of determining B-cell numbers than looking at the cellular level. It may also allow us to stratify patients into further sub-groups.

CXCL13 and sICAM . These molecules have been measured in the blood and proposed by other researchers as surrogate markers of B-cell pathotype in the synovium. We have both the blood samples and synovial tissue from patients so we can confirm if the theory is correct. Replacing the biopsy with a blood test would be beneficial for patients and the NHS

The plan is to

- evaluate whether these measures of B-cells can be used to predict patients' response to RTX (stratification)

- measure whether the number of B-cells in the joint (synovial tissue) is affected by treatment and if a drop in B-cell number correlates with the patients' response to treatment (mechanism)

- use new methods have been developed in recent years based on computer programs for what is called "deep learning". These computer programs process images in a way that has some similarities with how the brain is thought to work, in that they are built up of successive layers that learn to recognize features. However, (despite what you may have heard in the media) these deep learning algorithms can't really think, and don't understand anything. For this project we have a chance to work with top informatics specialists in the University of Edinburgh who are expert in constructing these algorithms.

The group were supportive of the proposal particularly as it ensures that best use is made of the samples and confirmed that if the project is funded by NIHR MPAG would be prepared to review progress of this research as part of our stratified medicine programme.

ACTION: GH to provide copies of information provided (including the lay summary we have drafted for the grant application) and comments from the group were requested by 21st November for submission to NIHR by the 28th of November.

2.6 ARUK funding strategy

One of our key objectives is to increase patient engagement, particularly at the hospitals where we are running clinical trials, here we have had some success but we are keen to utilise the programme we have developed in more areas of the country.

We would like to develop the 'meet the researcher' model used for the QMUL BBQ and link engagement events with social interaction. CA advise that ARUK is offering training and could help support any institutions were struggling with implementing PPIE activities. CA will be at Cardiff in the new year and could help promote the MATURA initiatives.

ACTION: GH & CA to liaise on site input

2.7 Future dates to note:

15th December 2016 Kellgren at 10 years, Manchester. DM explained that this is an afternoon event to celebrate the centre's 10-year anniversary and we will use it as an opportunity to engage patient in the prospects of stratified medicines for RA and the STRAP trial using our posters and leaflets.

6th February 2018 MATURA Scientific Symposium Manchester

28th February 2018 is the deadline for an article for Spring edition of NRAS magazine, ZI suggested including the general benefits of research.

20th June 2018 QMUL Science Festival