PPI MEETING DETAILED DISCUSSION NOTES FOR FINAL CONSENSUS MEETING

PROTOCOL 2 – IV versus JOINT INJECTION

1) IS AGE AN ISSUE?

Some parents could not imagine choosing either option for their child, but the group said that many children have had these routes through clinical necessity and have coped. It was suggested that there should be no lower age limit as all children need treating, although some parents felt that toddlers might not tolerate IV cannulation. Younger children might also find GA for joint injections scary (and some families were particularly reluctant to be randomised to a protocol which included this). They would also want to avoid several GAs in quick succession. It was suggested that children should be provided with psychological support to prepare them for any treatments, research specific or otherwise. Older children should be offered opportunity to have gas and air/ Entonox sedation versus GA in the joint injection arm where possible.

2) HOW MANY JOINTS ARE TOO MANY?

It was suggested that there should not be a specific minimum number of joints to be treated but the maximum suggested in the study protocol (i.e. 10) was too many for joint injections alone. Families also said that their clinician rarely treats more than 3-4 joints in one procedure. Children with multiple joints would likely need a GA on more than one occasion with associated risks. One mother said their child has systemic JIA but no affected joints so they would not be suitable for joint injections, although the chosen protocols would exclude such a patient. It was also suggested that severity was more important than the number of joints affected and that if the child had particularly severe joints they might be more/less willing to participate. It was also raised that IACI sometimes work well in one joint but not on other joints and the group were unclear what would happen in this situation.

3) HOW IMPORTANT ARE PAST EXPERIENCES?

Past experiences with treatment were seen as important in the decision to join a randomised trial in the future. If the child had received a particular treatment in the past that hadn't worked the family may be reluctant to try it again. However, some felt that if the child was

not as severe and had just mildly inflamed joints, they would be willing to give a treatment another chance with assurance that they would be offered something else soon after if it didn't work.

They also said that if they were relatively 'well' on the regime they were on, they would be reluctant to be randomised to a different treatment just on the chance that something might work better. The Young People in the group also agreed with this.

PROTOCOL 8 – ALL FOUR DELIVERY ROUTES

1) It was agreed that the issues mentioned for protocol 2 were similar for protocol 8, mainly because joint injection is the comparator for both. However, there were also concerns about treating younger children with muscle injection, as some heard that it might be painful and they also suggested that tablets could be hard to administer for younger children. Equally, parents felt that as children get older treatment compliance can also be challenging.

OTHER QUESTIONS/CONCERNS:

1) Protocol 8 says that children with active infection are excluded? One parent explained that their child always has infection, so would always be excluded (therefore it would be important to clarify what "active infection" means)

2) Often families aren't given all the information on risks and side effects of treatment and parents think this is very important. Parents are unhappy with the current level of information provided about side effects. One parent wasn't told about the impact of steroids on osteoporosis and their child has needed a hip operation as a result of the effect.

OUTCOMES

There was a discussion about how people would know the treatment had been effective. The following were mentioned in relation to this: pain; fatigue / energy; growth; skin colour; overall movement / freedom of movement; appetite; being able to dress independently; reduced irritability.

STUDY MATERIALS

Videos would be a useful way to present information to both parents and children.
Animation or real-life videos were both viewed to be acceptable. They felt that it would be

important to know from the video what would be involved in taking part in the trial and what would be happening. The characters would need to be realistic if an animation was done. Parents said that a trial website with comprehensive information would be a bit much for children if it included information on risks etc. but equally, the parents would want to know the risks of all treatments. One parent mentioned resources that had been developed by (or with) the Scottish Network Arthritis Children where the videos related to 'what and why' and were seen to be potentially useful.
(https://www.whatwhychildreninhospital.org.uk/videos-all)

RECEIVING THE TREATMENT

Parents felt it would be useful to tie in study visits with their usual clinic appointment so that there is less burden. A number of parents mentioned that they wouldn't want to go elsewhere if a treatment / study visit couldn't be offered at their usual hospital - familiarity and consistency was important.

INCENTIVES

Parents said vouchers were a good idea to keep CYP engaged in the process of a study e.g. Amazon. Parents felt that children shouldn't receive the same amount of money as their parents as they might not understand the value so much. It was suggested that if a parent got £75 for a half day of involvement that the child should get £50. CYP disagreed and felt they should get just as much as parents. Parents suggested that children of all ages should be given the same and that the value should not be increased by age as that is unfair.

RANDOMISATION

Some of the parents found the concept of randomisation quite tricky to understand. There was a focus from parents on them relying on the clinician's experience. One example of a way of explaining the randomisation suggested was that potentially CYPs could be treated with different treatments anyway if they saw different clinicians because there is not agreement on the best treatment. This explanation was well received and one parent suggested that this made a trial more acceptable.

BEING PART OF A TRIAL COMMUNITY

People seemed to like the idea of being part of a trial community (although with no access to other participants) and liked the idea of updates on the trial for participants. The idea of a quarterly newsletter that would include numbers recruited, target, progress, and useful info was well received. Social media engagement was mentioned but there wasn't a lot of response to this – there were concerns about how this might impact the trial.

FINDING OUT ABOUT CLINICAL TRIALS

No-one had heard of the 'OK to Ask' or the 'I am Research' campaigns. It was suggested that these need to be run repeatedly. Parents talked about a scarcity of information about what research was available to take part in and that they usually heard about things through their consultant, although one parent, as a result of attending the meeting heard about another research study of interest.

DISSEMINATION

Families wanted to be updated on study results at the end of a trial but wanted this in a format whereby they could choose whether to find out more information. One parent recognised the potential sensitivity of receiving study results, this parent thought that they might not want to hear about the results if the treatment their child had been allocated to have not been effective.

GOING FORWARD FOR THE SIRJIA PPI GROUP

Families would like to be updated on progress of the project e.g. what the key points from today's discussion was and whether a funding application is developed. This is especially pertinent given that in practise we asked families to wait until the end of the HCPs session but in view of travel arrangements they all had to leave prior to the planned group debrief.

CYP/ Parents CONCLUSION

The following points were discussed:

•Parents stated that they couldn't imagine randomisation as parents wouldn't want their child to have IV or IA (protocol 2).

•Parents/patients discussed how psychological support would be needed for patients with needle phobias.

•Whether GA is used or not should be a choice.

•It was stated that IV isn't suitable for toddlers.

•Parents wanted the maximum number of joints but not exact joints in the protocol

•It was discussed that the severity of joints was important:

If a patients JIA was less severe they were more likely to want to use treatment that has been used before.

If a patients JIA was more severe they would be more willing to try a different route of CS.

•Parents/patients discussed how it was important that they are fully informed of details of the trial and any side effects, etc.

•Parents/patients discussed how if a patient had a previous treatment that has worked they would be less inclined to participate in the trial.

•Parents/patients stated that clarification was needed on the statement in protocol 8 "excluded if active infection".

HCPS DISCUSSION AS PART OF THE FINAL CONSENSUS MEETING

PROTOCOL 2 – IV V JOINT INJECTION

INCLUSION/EXCLUSION CRITERIA

IA steroid injection response from baseline to response at 6 weeks was used and agreed on to detect minimal important difference.

If oligo-arthritis patients are excluded from protocol 2 then this would reduce the number of available patients from the screening numbers. It was also suggested that if in a future trial patients with oligo-articular JIA are excluded but patients with poly-JIA are included, it would be much easier to see drops in disease activity measures of 30-50. If we wanted to see a three-fold difference in scores it was suggested that this would need a sample size of around 100. If we assume that 77% of the 35 patients with data available are patients with oligo-articular JIA then we should be doing power calculations on the polyarthritis patients only to get a more realistic idea of available patient numbers. However, we would lose 32% of patients based on screening log.

(NOTE These figures were not based on direct calculations and are recorded simply as part of the discussion.)

There is a possibility that the data may be skewed as data was not analysed on other treatments patients received. For example, a patient taking a biologic and MTX may be responding better than patients taking MTX alone.

The group agreed that patients with severe active skin disease/ severe active psoriasis should be excluded in this protocol. The group agreed that an objective skin assessment should be used to assess this criterion and perhaps other clinical trials may have assessments that can be used in this trial. It was suggested that skin disease was assessed objectively rather than subjectively.

The group discussed whether the protocol excludes the use of other medications. It was explained that dermatologists may be reluctant to give medications in combination with steroids.

The group did agree that medications allowed/not allowed will need to be same in all arms of the trial. It was argued that the protocol should allow treatment with MTX but not to allow treatment with biologics. It was agreed that it could be ok to allow patients to enter the trial if they are currently taking biologics but not to allow patient to start biologics on entering the trial.

The group discussed the fact that it would be difficult to recruit to recruit systemic patients into the trial.

If we were to capture both new patients and patients flaring then this may result in difficulties in the eligibility criteria between both sets of patients which could lead to reducing the pool of available patients. Ideally new patients would be preferable, however the sample size could then be too small and in clinical practise many flaring patients receive CS.

CYPs with enthesitis only should possibly be an exclusion. For patients to be eligible they would need to be able to have joint injections. This principle would also include those with tendonitis. It was then agreed that CYP with polyarthritis who also have active enthesitis and tendonitis as well as arthritis may be included.

The group agreed that active cervical spine disease in the face of polyarticular disease would be excluded although the specific reasons for this were unclear as there would not be a placebo arm. The group agreed that active TMJ would not be exclusion.

Regarding age, one initial suggestion was to exclude people under 2 years old, however it was then agreed by the majority of HCPs that there should be no rigid exclusions in regard to age as all age groups have JIA and none should be disadvantaged without good reason. The group also agreed that further discussions need to take place regarding upper age limit.

The number of maximum joints was briefly discussed before it was suggested that this was a very difficult issue to decide in a discussion and therefore would need to be discussed as a single topic later.

It was noted that patient's response to treatment varies and that some patients respond after 2 weeks. This could be captured by active electronic recording of disease experience features and potentially by 2 weekly visits for the first 6-8 weeks.

The fact that patients with polyarthritis are normally started on MTX was noted with the suggestion that MTX could be started at the same time as the steroids in this group of patients.

PROTOCOL 8 – ALL FOUR DELIVERY ROUTES

PRIMARY OUTCOME

The group agreed with cJADAS as the primary outcome. The group agreed though that further discussion should take place to understand what the clinically significant reduction in JADAS score would be.

The group asked whether we should be looking at an equivalence or significant difference between study arms.

INCLUSION/EXCLUSION CRITERIA

No specific ages were debated however it was agreed that for the IM injections, age should be considered due to pain. In inclusion 1, the timescale for flare needs to be clarified and it was queried if exclusion criteria 1 was actually required.

DOSAGE

It was asked how to get the equivalent dosage of steroid over the 3 different treatments; the response was that the same dosage may not be needed due to different mechanisms involved in the different treatments. It was noted that the number of days and the doses of IV and IM needs to be clarified.

LENGTH OF TIME

It was argued that the IV route does not necessarily have to be 3 days, and that it could in fact be a single treatment – this is something which could be considered, but something that is not in common practise.

OTHER NOTES

Regarding joint injection, it was claimed doing this within 2 weeks would be tricky even for large units.

It was argued that side effects of the treatments are important, as is cost effectiveness; if the trial is conducted and the results show very little difference, perhaps the cheapest treatment should be used in future.

The group agreed that age is an important factor for IM injections, patients need to be old enough to understand why they are having painful injections. The group agreed that further discussion needs to take place regarding this. The group agreed that the number of days and doses of IM needs further discussions.

The group agreed that further discussions need to take place regarding how to ensure there are equivalent doses between the 3 treatment groups, although it was also felt that the current regimes should be compared rather than calculating steroid dose equivalents. There are differences between genomic and non-genomic effects so different doses may have different effects. Collecting samples for pharmacogenetics should be considered in the trial.

The group agreed that risk of AVN should be discussed further.

The group agreed that cost-effectiveness should be an important secondary outcome and would be helpful if all 3 treatment arms show the same results.

The group also agreed that safety and tolerability of all routes should be secondary outcomes.

The group were concerned that if they drop an arm out of clinical practice due to apparent lack of efficacy when this could have been as the patient hadn't been dosed appropriately.

The following points were discussed:

•Oral doses – votes in protocol survey.

•IA doses – doses are in previous protocol details.

•Age restriction would be considered for IM (2 years?)

•How to go about getting an equivalent dose of steroids within each treatment group?

•Dose of IM needs to be decided.

•Average time of IA injections delivery is between 18-20 days and this would cause a delay in receiving any treatment, as opposed to other routes where more immediate treatments can be given. It would be important that being involved in a study did not actually disadvantage

patients by worsening their time to treatment and therefore their initial suffering. The study protocol should therefore stipulate a maximum appropriate time within which to administer IA CS.

•When asked what would be a clinically relevant difference in JADAS scores, HCPs stated that because JADAS isn't calculated in practice they are unaware of what a minimally important clinical difference would be.

•Whether IA vs IV should look for equivalence rather than superiority.

•Whether cost effectiveness and side effects should be included as a secondary outcome.

•Whether a timescale of flare is required within the inclusion criteria.

•Amount of IV steroid to use.

SURVEY DISCUSSION

Concern was expressed over what clinical meaningful difference in the JADAS would be accepted for a steroid remission induction trial and whether enough patients would be able to achieve this within 4-6 weeks. It was suggested that this detail be revised to achieve the difference by six weeks rather than 4-6 weeks.