Extended data from:

Prior elicitation of the efficacy and tolerability of Methotrexate and Mycophenolate Mofetil in Juvenile Localised Scleroderma

Appendix S1 Participants in prior elicitation meeting

A meeting was conducted with the aim to characterise efficacy and tolerability information on the two treatments, MTX and MMF, into useable prior distributions through expert opinion. The following was agreed as a definition for a clinical expert:

1. Rheumatologist/dermatologist with expertise in looking after patients with JLS,
2. Treated 10 or more CYP below the age of 18 with JLS in the last 2 years,
3. Experience in prescribing MTX for the treatment of JLS,
4. Experience in prescribing MMF for the treatment of JLS,
5. Willingness to participate in a meeting to elicit their opinion on MTX and MMF.

Invitations were sent to potentially eligible clinicians through a number of societies and professional organisations. These include: United Kingdom (UK) Juvenile Scleroderma Working Group, Paediatric Rheumatology European Society Scleroderma Working Party, Ped Rheum international bulletin board, in North America via a JLS study group (CARRA SCORE) and via the British Society of Paediatric & Adolescent Rheumatology. Direct invitations were also sent to 9 individuals who had published sentinel research on JLS.

Of a total of 54 clinicians who replied, 28 fulfilled the eligibility criteria and were able to participate on the date of the prior meeting. Eligible participants originated from various regions of the world; specifically Europe (14), North America (9), South America (1), Asia (2), Africa (1), Middle East (1). Twelve clinicians were randomly selected with a criterion of ensuring the meeting was made up of six UK, four European and two international clinicians, with a minimal number of two representatives from dermatology. All invited participants attended the prior elicitation exercise day on 6th June 2019 at the Alder Hey Children's NHS Foundation Trust, Liverpool, UK.

Participants were sent a literature pack containing up-to-date information on the two treatments and the disease area. The literature contained a summary of a literature search of efficacy and tolerability of MTX and MMF performed by systematic review researchers at Keele University, summary of literature on corticosteroid regimes in JLS, background to the prior elicitation and mLoSSi.

Clinicians who participated in prior elicitation meeting

Prof. Tadej Avcin, Professor of Pediatrics, University Children's Hospital, Ljubljana, Slovenia

Dr Bisola Laguda, Consultant Paediatric Dermatologist, Chelsea and Westminster Hospital, UK

Dr Valentina Leone, Consultant Paediatric Rheumatologist, Leeds Children's Hospital, UK

Dr Kathryn S Torok, Associate Professor of Pediatrics, UPMC Children's Hospital of Pittsburgh, USA

Dr Suzanne Li, Professor of Pediatrics, Hackensack University Medical Center, Hackensack Meridian School of Medicine, USA

Dr Marina Anderson, Honorary Consultant in Rheumatology, Aintree University Hospital, UK

Dr Francesco Zulian, Associate Professor of Pediatrics, University Hospital of Padua, Italy

Dr Flora McErlane, Consultant in Paediatric Rheumatology, Great North Children's Hospital, UK

Dr Jordi Anton, Head of Division, Pediatric Rheumatology, Hospital Sant Joan de Déu, Barcelona, Spain

Dr Ivan Foeldvari, Head of the Hamburg Centre for Pediatric and Adolescence Rheumatology, Hamburg, Germany

Dr Lindsay Shaw, Consultant Paediatric Dermatologist, Great Ormond Street Hospital & Bristol Children's Hospital, UK

Dr Jessie Felton, Consultant Dermatologist, Brighton and Sussex University Hospitals & Royal Alexandra Children's Hospital, UK

Appendix S2 – Inclusion criteria for a clinical trial of MTX and MMF defined before elicitation exercise

Children and young people (CYP) aged 2-18 years with JLS defined as:

- onset of disease before 18 years of age,

- diagnosis of JLS made by either specialist rheumatologist or dermatologist (includes all subgroups of JLS),

- systemic immunosuppression indicated in the opinion of specialist clinician,

- MTX and MMF naïve,

- Active disease defined as any new or enlarging lesions and erythema or induration of lesions confirmed by score ≥4 on mLoSSI at baseline.

Appendix S3 Detailed methodology of elicitation process

An interactive session was delivered introducing Bayesian methodology and its role in this research project (presentation included in the Supplementary materials). Two illustrative examples were provided; the first of which illustrated probability density functions to demonstrate what prior and subsequent posterior distributions look like. This example also showed how data, when incorporated with the prior distribution, would affect the resulting posterior distribution.

The second example was a mock elicitation using a hypothetical example that replicated the structure of the real elicitation. This was to show the questions used for the elicitation of expert opinion and provided all clinicians the opportunity to become familiar with the questions and the interpretation of the resulting distributions before the actual elicitation. Interactive software was used during the mock elicitation to provide a live update of opinions on prior distributions to demonstrate how different answers to the questions provided altered the shape of the distribution.

Questions 1 & 2 concern the expert's opinion on the efficacy of MTX. Question 1 provided the experts most likely value of the true proportion of successful treatment on MTX, whilst questions 2 provided information the uncertainty about the true proportion of successful treatment. These two questions allow to find the underlying parameters of the Beta distribution used to model p_{MTX} and hence characterise each expert's opinion on the probability of successful treatment on MTX.

Questions 3 & 4, once combined with questions 1 & 2, provided information on the expert's opinion on the log odds ratio, $\theta_{efficacy}$. Question 3 compares the two treatments directly. An answer of 0.5 showed the expert was unsure of which treatment showed greater effectiveness. If an expert deemed MMF to be better, their answer would lie anywhere between (0.51, 0.99) where being further away from 0.5 suggested a stronger opinion. On the other hand, if an expert deemed MTX to be superior in efficacy, their answer would lie between (0.01, 0.49) with a stronger opinion being further away from 0.5.

Question 3 provided an upper bound for the answer to Question 4 i.e. the answer to Question 4 could be no greater than 1 - Question 3. Question 4 required thought since the direction in which the question was asked was reversed compared to Question 3.This was to prevent any leading questions where the clinician would subconsciously favour MMF since both questions were asked in favour of MMF. Interpretation of answers to Question 4 were dependent on the answers given to Question 3. If a clinician wanted to show their belief on MTX was the same as their belief on MMF, Question 3 would be answered with 0.5 and Question 4 with 0.01.

Questions 1 – 4 provided sufficient information to characterise expert opinion on the efficacy of both MTX and MMF. Two further questions, Question 5 and 6, were included to ensure the correct elicitation of the prior distributions on MMF. These two questions were similar to Questions 1 and 2 but with regards to MMF rather than MTX. They provided a

ballpark area of where the weight of the prior distribution derived from the distribution of the log odds ratio, $\theta_{efficacy,}$ should be. In the case where there was a large discrepancy between the derived and elicited distributions on MMF, a discussion with the expert was required to determine the source of discrepancy and possibly confusion. In the case where the derived prior distribution on MMF did not provide a satisfactory characterisation on an expert's opinion, the elicited prior distribution by using questions 5 and 6 was taken forward as the prior distribution for that individual.

Questions 7 - 12 then are identical except that they concern the tolerability rather than efficacy of the two treatments.

Questions asked to elicit prior distributions

1. Assuming the patient tolerates MTX, What do you think the 12-month success rate for children with JLS treated with MTX in combination with corticosteroids is?

2. Assuming the patient tolerates MTX, provide a proportion such that you are 75% sure (25^{th} percentile) that the true 12-month remission rate on MTX & corticosteroids exceeds this value.

3. Assuming the patient tolerates the drugs, what is the chance that the 12-month remission rate on MMF/steroids is higher than that on MTX/steroids?

4. Assuming the patient tolerates the drugs, what is the chance that the 12-month remission rate on MTX/steroids exceeds that on MMF/steroids by more than 10%?

5. Assuming the patient tolerates MMF, what do you think the 12-month success rate on MMF & corticosteroids is?*

6. Assuming the patient tolerates MMF, provide a proportion such that you are 75% sure (25^{th} percentile) that the true 12-month remission rate on MMF & corticosteroids exceeds this value.*

7. What do you think the 12-month tolerability rate for children with JLS treated with MTX in combination with corticosteroids is?

8. Provide a proportion such that you are 75% sure (25th percentile) that the true 12-month tolerance rate on MTX & corticosteroids exceeds this value.

9. What is the chance that the 12-month tolerability rate on MMF/steroids is higher than that on MTX/steroids?

10. What is the chance that the 12-month tolerance rate on MTX/steroids exceeds that on MMF/steroids by more than 10%?

11. What do you think the 12-month tolerance rate on MMF & corticosteroids is?*

12. Provide a proportion such that you are 75% sure (25th percentile) that the true 12-month tolerance rate on MMF & corticosteroids exceeds this value.*

** - Denotes redundant questions.*