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Executive Director

Letter of support for Eye tracking to be used to stratify populations of people with Autism Spectrum Disorder (ASD)

On 14 September 2015 the Applicant EU-AIMS Consortium (IMI) requested follow-up qualification advice for Eye-tracking methodologies to be used to stratify populations of people with Autism Spectrum Disorder (ASD) pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 03 - 06 November 2015, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on 16 – 19 November 2015, the CHMP adopted the advice to be given to the Applicant.

The European Autism Interventions - A Multicentre Study for Developing New Medications (EU-AIMS) is a project funded and run under the Innovative Medicines Initiative (IMI). Among the aims of this project is to develop and validate new methodologies for the advancement of novel therapies to treat Autism spectrum disorders (ASD). The project is managed by an international consortium of research academic institutes and industry.

On the basis of the qualification advice, the Agency is issuing this Letter of Support to the EU-AIMS Consortium (IMI) to encourage the further study of Eye-tracking tools to be used to stratify populations.

Eye tracking -Implicit False Belief

The stimuli and procedure are taken from Southgate et al (2007) and Senju et al (2009) and consist of four familiarization trials, followed by one test trial (false belief 1, FB1). The general set-up of the scene is the same for all trials: an actor is seated behind a panel containing two windows, and in front of each window there is an opaque box with a lid.

The purpose of the familiarization trials is to show that the actor's goal is to obtain the ball and to teach the volunteer the contingency between the windows being illuminated and a corresponding "chime" sound and the subsequent opening of one of the windows by the actor.

In the FB1condition, the puppet appears at the centre of the stage, deposits the ball in the left-hand box, and returns to the centre. The puppet then goes back to the left-hand box, opens the lid, takes the ball, and places it in the centre. The puppet then opens the lid of the right-hand box, retrieves the ball, puts it inside the box, and closes the lid. The puppet then returns to the left-hand box (while the actor's attention follows), closes the lid, and disappears. At this point, the sound of a phone ringing is played and the actor turns around as if they are attending to this sound. As soon as the actor turns away, the puppet reappears, opens the right-hand box, retrieves the ball, closes the lid, and disappears with the ball. As soon as the puppet disappears, the phone stops ringing and the actor turns back. Then, the windows are illuminated and a chime sounds. After that, the actor remains still for the following 5 seconds. Two controls will be incorporated to eliminate any cues that might affect participants' looking behaviour. First, the actor wears a visor, which makes the actor's eyes invisible and prevents the participants from following, or attempting to follow, the actor's eye gaze. Second, after turning back toward the stage in the test trials, the actor keeps their head centred and makes no movement, so as not to give any cues as to where they would search.

If the participant can represent the actor's false belief, they should be able to deduce that (a) the ball is no longer in the right-hand box, but (b) the actor did not see it disappear, therefore (c) they should have the false belief that the ball is still in the right-hand box. On the basis of this false belief attribution, participants should predict that (d) the actor will reach through the right-hand window once the window is illuminated.

Emotional Matching Task

A computerised emotion-matching task (Uljarevic and Hamilton 2013) will be used that taps recognition of basic emotions of positive and negative valences and varies both stimulus presentation and response time. Each trial consists of a set of three pictures and participants are asked to match the target picture with the three other pictures. The correct choice expresses the same emotion as the target but differs in other features such as identity or angle of view. Accuracy and reaction time scores serve as primary depending variables. Eye-movements will be concurrently recorded to test whether emotion recognition deficits in the ASD group are mediated by diminished spontaneous attention on the eyes.

In a second condition, participants are shown pictures of faces with positive and negative emotion expressions (happy, anger, fear, sadness). Here, we will explicitly cue fixation on the eyes by presenting a fixation cross at eye-level prior to each trial (Dalton et al 2005). By recording galavanic skin response/heart rate, this condition aims to test whether attention of the eyes elicits hyper- or hypo-arousal in children and adults with ASD compared to the typically developing/ learning difficulties(TD/LD) groups.

Naturalistic Viewing of Social Scenes

A set of static and dynamic social scenes was selected to study anomalies in spontaneous social attention associated with ASD. These anomalies are hypothesized to serve as a potential surrogate outcome measure, sensitive to change. The battery includes the following sets of stimuli:

- 4 pop-out still images presented for 15 seconds each, total 60 seconds;

- 4 still images of naturalistic social scenes (photographs depicting e.g., parent and child, interacting children or adults in naturalistic settings) presented for 15 seconds each, total 60 seconds;

- 4 still images taken from the "50 faces set", total 60 seconds

- 2 scenes from "pingu" movies (120 seconds).

- All stimuli and movies described above are taken from the infants-at-risk eye-tracking battery and are suitable for all targeted age and ability ranges.

- "Welcome to the Dolls' house", (shortened, 2 minutes, Rice et al 2012)

- **Schedule A** additionally includes the "music booth" scene taken from the movie "Before Sunrise" (about 1 minute) and, at the two UK sites, clips from "Who is afraid of Virginia Wolf (Klin et al 2002). The "Virginia Wolf" clip can only be included at UK sites due to the high and relevant verbal component. The scenes were selected because they contain a host of social-communicative and social-emotional cues.

Visual fixation patterns on social versus non-social features of scenes (including first fixations, average fixation during, total fixation time, scan paths) serve as the key dependent variables; Relation of direction of visual attention to low-level (e.g., motion, luminance) and high-level (e.g., social vs. non-social) scene features will be the secondary outcome measures.

Gap Overlap Task

The Gap Overlap task (adapted from Elsabbagh et al 2013, Landry and Bryson 2004) is a gaze contingent paradigm that measures visual attention shifting between a central and a peripheral stimulus in one of three conditions: i) Gap, in which the central stimulus disappears 200 milliseconds before the appearance of the peripheral target; ii) Baseline, in which the central stimulus disappears simultaneously with the appearance of the peripheral target; iii) Overlap, in which the central stimulus remains on the screen during peripheral target presentation. Key-dependent variables: latency to shift attention to the peripheral stimulus in the Gap versus baseline conditions (Facilitation) and Gap versus Overlap conditions (Disengagement).

EMA encourage the primary study objective of the EU-AIMS Longitudinal European Autism Project (EU-AIMS LEAP) to identify biomarkers for stratification of patients with distinct subtypes of ASD and to examine how the clinical ASD phenotype and biomarker profile develop over time through re-assessment after 12-24 months and by using an accelerated longitudinal design. Inclusion of psychiatric comorbidities is agreed upon considering the high prevalence of comorbid conditions in the ASD population. Although heterogeneity should be minimized in confirmatory studies, the present study should allow for more information to be gathered regarding the influence of these conditions on the changes secondary to intervention.

Sincerely,

Guido Rasi
Executive Director
European Medicines Agency