



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 December 2015
EMA/794534/2015
Executive Director

Letter of support for Measures of executive function and basic emotions to be used to stratify populations of people with Autism Spectrum Disorder (ASD) and predict clinical outcome

On 14 September 2015 the Applicant EU-AIMS Consortium (IMI) requested follow-up qualification advice for measures of executive function and basic emotions to be used to stratify populations of people with Autism Spectrum Disorder (ASD) and predict clinical outcome 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 the following panel of task performance measures to measure cognitive deficits in paediatric patients with ASD and their potential to stratify patient groups. The data generated by the EU-AIMS LEAP study will be likely not sufficient for a use as outcome measures unless data will be replicated. Therefore, we encourage the independent study of these methodologies.

Probabilistic Reversal Learning Task

The Consortium acknowledged the concerns raised regarding the originally proposed version of a probabilistic reversal learning task based on D'Cruz et al (2013) and during the Discussion Meeting with the Qualification Team, the Consortium proposed to replace it with the task of den Ouden et al, (2013). In brief the task has been used in nearly 700 healthy adult volunteers. It is also currently used in another large-scale consortium project with children with ADHD ("NeuroImage").

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union



The neurobiological contribution is better understood. Seminal electrophysiological studies showed that dopaminergic (DA) neurons in the midbrain increase firing to unexpected rewards (Schultz et al., 1997; Fiorillo et al., 2003). Phasic DA is taken as a reinforcement signal. Pharmacological and fMRI studies in humans have shown that DA drugs enhance learning from reward vs. punishment.

On the other hand, serotonin is linked to learning from negative events/ punishments. For example, after administration of serotonin reuptake inhibitors (citalopram) healthy volunteers shift more often way from stimuli that result in a loss (Chamberlain et al., 2006) whereas tryptophan depletion selectively improves prediction of punishments (Cools et al., 2008),

Using a candidate gene approach, the den Ouden et al study demonstrated a double-dissociation effect of a dopamine transporter (DAT1) and Serotonin transporter (5HTT) polymorphism on performance on probabilistic learning. The DAT1 genotype affected the influence of prior choices on perseveration; the serotonin transporter genotype affected behavioural adaptation after losses – thus at least indirectly implying a differential contribution of these two neurotransmitters.

Task summary: participants are presented with two stimuli (blue and yellow patterns) in two out of four randomly selected locations (left, right, top or bottom of the screen). In each trial, participants are instructed to select the stimulus that is usually rewarded, upon which positive or negative feedback is given immediately. Previous versions of the task used the words 'correct', 'wrong' alongside positive/negative sounds, and/ or positive/ negative emotions. In the current version a stack of coins (ascending/ descending) are used together with the positive/ negative sounds. Points and monetary rewards are commonly used in probabilistic reversal learning tasks (D'Cruz et al., 2013) and our pilot experience with children, adolescents and adults with ASD suggest that winning points is an attractive incentive. Participants are instructed that the identity of the correct stimulus can change, but receive no information as to how often such a change might occur. Choosing the correct stimulus (defined as the stimulus chosen on the first trial) results in a 70:30 ratio of reward/punishment. Thus, on 30% of trials volunteers receive "misleading" feedback. Each participant completes a pseudorandom fixed sequence of 80 trials.

After 40 trials the reinforcement contingencies are reversed, so that the frequently rewarded stimulus now becomes frequently punished and vice versa.

In keeping with other reversal learning tasks, the formal learning criterion is eight consecutive correct responses. Win-stay trials are trials in which the volunteer picks the same stimulus as they did on the previous rewarded trial. Lose-shift trials are trials in which the subject shifts the response after a punishment. Perseverative errors are defined as two or more consecutive incorrect choices of the previously rewarded stimulus; i.e. volunteers erroneously stay with the previously correct stimulus, despite punishment.

Spatial Working Memory

The "Find a Phone" task is an adaptation (Sjöwall et al 2013) of the Cambridge Automated Neuropsychological (CANTAB) Spatial Working Memory test (Owens et al 1990). In this version, 3 to 8 telephones are shown on the computer screen. Participants are required to find which of several telephones is ringing with the explicit instruction that a phone never rings in the same location in which it has rung before. The number of times the participant returns to a phone that has already rung is

used as an index of working memory deficits. The task difficulty gradually increases (number of telephones increasing, e.g., from three, to four, to six, to eight - indicating working memory load). At each level of difficulty, participants are required to successfully solve at least four trials. Modifications include changes in the surface features and addition of a break-out clause to reduce frustration in participants who find the task difficult. Errors and strategy scores serve as the main outcome measures.

Animated shapes, theory of mind task, Verbal Narratives

Participants are shown eight short video-clips from among the original Happé-Frith animations (Abell et al 2000). They include a) four animations showing an interaction with thoughts and feelings (theory of mind, ToM), b) two animations depicting a simple goal-directed interaction (GD), and c) two animations showing random movements (R). Participants are instructed to give a verbal description of what they think is happening in the video. The verbal narratives will be audio-recorded, transcribed and analysed for “appropriateness” (i.e., correct inference of the underlying scenarios) and “intentionality” (i.e., use of mental state terms) using the scoring system described by Castelli et al (2000). At least 50% of narratives shall be scored by a second rater, blind to group status and schedule. Inter-rater reliability will be periodically monitored.

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