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Executive Director

Letter of support to explore Clinical Outcomes Assessments utility to measure clinical symptoms in people with Autism Spectrum Disorders

On 14 September 2015 the Applicant EU-AIMS Consortium (IMI) requested follow-up qualification advice for Clinical Outcomes Assessments to measure clinical symptoms in 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 and use of the following clinical outcome scales in people with ASD.

Social Responsiveness Scale, 2nd Edition (SRS-2)
The SRS (Constantino and Gruber 2005) is a quantitative parent-report measure of autistic traits in 4- to 18-year-olds. It comprises 65 items, which resolve into 5 factors that map onto the two key domains of the ASD diagnosis, using a ‘‘0’’ (not true) to ‘‘3’’ (almost always true) point Likert scale generating one total score (max. 195). The questions focus on the child’s behaviour during the past 6 months and can be completed in 15–20 minutes. The SRS can be used both as a screener and as an aid to clinical diagnosis of ASD, particularly less severe forms like Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS). Total raw scores can be transformed into T-scores in order to provide the relative normative position of any proband regarding autistic traits. The second edition also includes a self-report form for adults aged 19 years and older and a preschool parent

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reported version (2.5 to 4 years). In the current study, parent-report forms will be used for all participants. In addition, self-report forms will be used in the adult groups. Frazier and colleagues applied confirmatory factor analysis and assessment of measurement invariance to a large (N = 9635) accumulated collection of reports on quantitative autistic traits using the SRS, representing a broad diversity of age, severity, and reporter type. The statistical power afforded by this large sample allowed relative differentiation of three factors among items encompassing social communication impairment (emotion recognition, social avoidance, and interpersonal relatedness) and two factors among items encompassing restricted, repetitive behaviour (insistence on sameness and repetitive mannerisms). Cross-trait correlations within this sample remained extremely high, i.e, in the order of 0.66–0.92 (Frazier et al 2013).

Children's Social Behaviour Questionnaire (CSBQ)

The CSBQ (Hartman et al 2006) is a 49-item parent-report questionnaire that was specifically developed to assess social behaviour problems across the whole ASD spectrum. The items describe a broad range of features that are typical of pervasive developmental disorders, particularly in its milder forms, and are composed of 6 subscales:

- Reduced contact and social interest
- Difficulties in understanding social information
- Stereotyped behaviours
- Fear and resistance to change
- Not optimally tuned to the social situation
- Orientation problems in time, place, activity (self-monitoring as in executive functions)

Repetitive Behaviour Scale-Revised

The Repetitive Behaviour Scale Revised (RBS-R) (Bodfish et al 1999) is an empirically-derived comprehensive survey of the entire spectrum of repetitive behaviours clinically observed and referred to in the DSM-5 diagnostic description of ASD. Parents or caregivers rate 43 behaviours on a scale of 0-3, where 0 indicates the behaviour does not occur and 3 indicates the behaviour does occur and is a severe problem. It showed discriminant validity in adults distinguishing participants with autism and learning disabilities from non-autistic participants with learning disabilities in the overall RBS severity score (Bodfish et al 2000).

Autism Spectrum Quotient

The Autism Spectrum Quotient (AQ) (Baron-Cohen et al 2001) is a self-report questionnaire to assess whether adults of average intelligence have symptoms of autism or associated with ASD. The test consists of 50 statements, each of which is in a forced choice format. Each question allows the participant to indicate "definitely agree", "slightly agree", "slightly disagree" or "definitely disagree". Approximately half the questions are worded to elicit an "agree" response from neurotypical individuals, and half to elicit a "disagree" response. The questions cover five different domains associated with the autism spectrum: social skills; communication skills; imagination; attention to detail; and attention switching/tolerance of change.

The Autism Spectrum Quotient – Adolescent Version (AQ-Adol) (Baron-Cohen et al 2006) is a parent-questionnaire, which includes almost the same exact 50 items as the adult version.

The Autism Spectrum Quotient—Children's Version (AQ-Child) (Auyeung et al 2008) is a 50-item parent-report questionnaire that aims to quantify autistic traits in children 4-11 years old. The AQ-Child was designed to be a parent-report questionnaire, since self-report by children might be

restricted by reading and comprehension difficulties. It was adapted from the adult and adolescent versions of the AQ, and items that were not age-appropriate in the adult questionnaires were revised accordingly. Items in the AQ-Child were kept as close to the AQ-Adult and AQ-Adol as possible, with most questions aimed at the same behaviours and five broad areas associated with autism.

Short Sensory Profile

The Short Sensory Profile (SSP) (Tomchek and Dunn 2007) is a 37-item parent-report questionnaire that probes for the effect of sensory processing anomalies on a person's ability to function in daily life. Item responses occur on a five-point Likert-rating scale from 1 (always occurs) to 5 (never occurs). The SSP is based on the Sensory Profile (Dunn 1999) and provides two sets of standard scores depending on how the items are clustered: (1) domain scores (i.e., Auditory, Visual, Vestibular, Touch, Multisensory and Oral Sensory Processing), as well as scores of Sensory Modulation, Behaviour and Emotional Response, and (2) factor scores (nine empirically derived factors).

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