Clinical Outcome Assessments Used/Recommended by the EMA and FDA for the Evaluation of Products to Treat Autism Spectrum Disorder

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Methodological Question Being Addressed

- This poster intends to address the methodological question of which clinical outcome assessments (COAs) to select and include in the evaluation of products for the treatment of autism spectrum disorder.

Introduction (Aims)

- Autism spectrum disorder (ASD) is a group of developmental disorders characterized by disturbance in language, perception and socialization. Autistic children have problems with verbal and nonverbal communication, troubles with social interaction, and present repetitive behaviors or obsessive interests [1]. Under the DSM-5 criteria, individuals with ASD must show symptoms from early childhood, even if those symptoms are not recognized until later. This criteria change encourages earlier diagnosis of ASD but also allows people whose symptoms may not be fully recognized until social demands exceed their capacity to receive the diagnosis [2].
- In the European Union, prevalence rates were estimated at a range between 30 and 63 per 10 000 (all forms of ASDs included) [3]. In the USA, the 2010 CDC estimates indicated that 14.7 per 1,000 8 year old were identified with ASD [4]. Prevalence is rising in both geographical areas.
- There is no cure for ASD. However, behavior and communication approaches, dietary treatments, and medication can be used to relieve some symptoms and behaviors.
- The objectives of this study were:
  1. To review which guidance were published by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to help industry prepare marketing-authorization applications for medicinal products for ASD treatment;
  2. To identify which products were approved specifically for ASD; and
  3. To find out about the use of clinical outcome assessments (COAs) in the approval process. COAs measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions.
     A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. Unlike biomarkers that rely completely on an automated process or algorithm, COAs depend on the implementation, interpretation, and reporting from a patient, a clinician, or an observer. There are four types of COA measures: patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO) measures.

References
1. Simms MD, Jin XM: Autism, Language Disorder, and Social (Pragmatic) Communication Disorder: DSM-V and Differential Diagnoses. Pediatr Rev 2015;36(8):355-62.
2. http://www.dsm5.org/Documents/Autism%20Spectrum%20Disorder%20Fact%20Sheet.pdf
3. http://ec.europa.eu/health/ph_information/dissemination/diseases/autism_1.pdf
4. http://www.cdc.gov/ncbddd/autism/data.html

Figure 1. EMA ASD Guideline

- Draft guideline available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500202650.pdf

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Guideline on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder (ASD)
Draft

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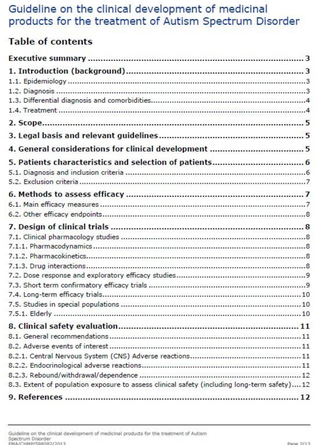
Comments should be provided using this template. The completed comments form should be sent to CNSWPSecretariat@ema.europa.eu.

Keywords	*Autism spectrum disorder, guidance, paediatric population, adults*



Guideline on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder

Table of contents

Guideline on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder
EMA/CHMP/598082/2013 Page 2/13

Conclusion

- The review revealed major discrepancies between the FDA and the EMA, with no products approved in Europe, while two were approved in the USA (however non-specific to ASD); no guidelines available in the USA, and draft guideline developed in Europe.
- COAs (ObsRO and ClinROs) played a major role in the evaluation of medicinal products approved for ASD in the USA. With globalization of research, more harmonization is needed between both agencies.

Disclosure: The authors report no conflicts of interest for this work

Methods

- This research was conducted on the FDA and EMA websites (http://www.fda.gov/Drugs/default.htm and http://www.ema.europa.eu/ema/ through a systematic manual review of ASD-specific EMA and FDA regulatory guidelines, product labeling and corresponding assessment reports or medical reviews.
- Mapi's PROLabels database (https://eprovide.mapi-trust.org/) was used for labeling claim identification. Off-label uses were not included.

Results

- The search of guidelines revealed that only the EMA Committee for Medicinal Products for Human Use (CHMP) has adopted a draft guideline on February 25, 2016 on the clinical development of medicinal products for the treatment of ASD (Figure 1). In this guideline, in the section devoted to "Methods to assess efficacy", the CHMP recommends the following:
  - Information should be obtained from at least one reliable informant and also from the subject (self-reported 'subject' rating scales) where this is possible. For children both the parent/carer and teacher should provide data where possible. In adolescents and adults the specified reliable informant will depend on the symptom and functional severity of the individuals being studied.
  - **Symptomatic scales**
    Symptoms should be assessed with scales validated for the full age range of patients to be studied. The use of the same rating scale for inclusion, efficacy and responder definition is recommended wherever possible. Scales based on clinician ratings using information obtained from reliable informants are most appropriate as primary efficacy measures. Both raters (clinicians) and observers (parents, caretakers, teachers etc.) should be adequately trained, including recording of data in observer diaries or into a database. Industry standard methods should be implemented to assess inter-rater reliability.
    The Autism Diagnostic Observation Schedule (ADOS, Lord et al. 1989) and the Childhood Autism Rating Scale (CARS, Schopfler et al. 1980) are validated for the assessment of core symptoms in ASD. These scales and others are in principle satisfactory if validated on test quality criteria (reliability, validity) and sensitivity to change is demonstrated.
  - **Functional scales**
    No validated scale of functioning has yet been clearly identified that would be specific to ASD. Functional scales developed for other conditions [e.g., ADHD) might have questionable applicability to ASD and might lack sensitivity for detecting a treatment effect in ASD patients. The development of a functional scale validated for autism is therefore encouraged. Adaption of an existing functional scale, developed for another condition but adapted as appropriate for the specific requirements of a clinical trial in ASD, is a possible approach.
  - **Global scales**
    The Clinical Global Impression - Improvement (CGI-I) scale is a well-established research rating tool applicable to psychiatric and neurological disorders that can easily be used by the practicing clinician (Guy et al. 1976; Busner et al. 2007). However it cannot be considered as a measure of function but as a global measure that reflects both core symptoms and functioning.
- The FDA has approved only two products with an indication of autistic disorders, i.e., risperidone and aripiprazole; two atypical antipsychotics for control of behavioral symptomatology. No products with this indication could be found on the EMA website. The main criterion of evaluation for the FDA approved products was *changes in symptoms* measured by COAs (Table 1).
  - Risperidone and aripiprazole used the Aberrant Behavior Checklist (ABC), a measure completed by caregivers (ObsRO), to assess changes in irritability (primary endpoint). Secondary endpoints involved the use of ClinROs: the Clinical Global Impression - Change (CGI-C) scale (risperidone), and the CGI-I scale (aripiprazole) to measure changes in irritability.

Table 1. Products Approved by the FDA with the indication of treatment of irritability associated with autistic disorder

INN	BRAND NAME	MARKETING AUTHORIZATION HOLDER	DATE OF APPROVAL	Labeling claim	Concept of Interest	COA measure	Type of COA	Endpoint positioning
risperidone	Risperdal	Janssen (NJ, USA)	02/04/2003	Short-term efficacy: S1: children and adolescents with autistic disorder (n=101) […] significantly improved scores on the ABC-I subscale and on the CGI-C scale compared with placebo. S2: children with autistic disorder (n=55) [...] significantly improved scores on the ABC-I subscale compared with placebo. Long-term efficacy: A pre-planned interim analysis of data from patients who completed the withdrawal study (n=32), undertaken by an independent Data Safety Monitoring Board, demonstrated a significantly lower relapse rate in the RISPERDAL® group compared with the placebo group. Based on the interim analysis results, the study was terminated due to demonstration of a statistically significant effect on relapse prevention. Relapse was defined as ≥ 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline of the randomized withdrawal phase).	Irritability	Aberrant Behavior Checklist (ABC)	ObsRO (caregivers)	Primary
						Clinical Global Impression - Change (CGI-C) scale	ClinRO	Co-primary in one study Secondary in the other study
aripiprazole	Abilify	Otsuka (MD, USA)	15/11/2002	S1: Significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo. S2: All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.	Irritability	Aberrant Behavior Checklist (ABC)	ObsRO (caregivers)	Primary
						Clinical Global Impression - Improvement (CGI-I) scale	ClinRO	Secondary

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