CLINICAL PRACTICE GUIDELINES

XXXX 2014 **MOH/P/PAK/xxx (GU)**

Draft
MANAGEMENT OF AUTISM SPECTRUM DISORDER IN CHILDREN AND ADOLESCENTS

Ministry of Health Malaysia

Malaysian Psychiatry Association

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2014 and will be reviewed in 2018 or sooner if new evidence becomes available.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grades of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for this Clinical Practice Guidelines (CPG) were from the Ministry of Health (MOH) and Ministry of Higher Education. There was active involvement of a multidisciplinary review committee (RC) during the process of development of this CPG.

A systematic literature search was carried out using the following databases: Guidelines International Network (G-I-N); Medline via Ovid, PUBMED, Cochrane Database of Systematic Reviews (CDSR) and International Health Technology Assessment websites. A search strategy to cover all aspects on management of autism spectrum disorders was developed in the Medline database and adapted to other databases. Search strategies were a combination of MeSH and keyword searches including abbreviations (refer to **Appendix 1** on an example of **Search Strategy**). Search was restricted to human studies; literature published in English language and the last ten years. If the evidence was insufficient, the period of publication was extended for another ten years. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. All searches were conducted from May 2012 till November 2013. Literature searches were repeated for all clinical questions at the end of the CPG development process. The aim was to identify any further relevant papers published before 28 February 2014 to be included. Future CPG update will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other CPGs on Autism Spectrum Disorder (ASD) such as i) Guidelines on treatment, diagnosis and clinical intervention for children and young people with autism spectrum disorder (SIGN 98-2007), ii) AMS-MOH Clinical Practice Guidelines 1/2010 - Autism Spectrum Disorders in Pre- School Children iii) Autism Spectrum Disorder by Ministry of Health New Zealand 2008, and iv) Autism: recognition, referral and diagnosis of children and young people on the autism spectrum by Royal College of Paediatrics and Child Health (2011). These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 27 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. (Refer to **Appendix 2**) The DG members had met 23 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC.These CPG are based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The evidence used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network.

On completion, the draft guidelines was sent for review by external reviewers. It was also posted on the MOH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, the HTA and CPG Council MOH Malaysia for review and approval.

OBJECTIVES

The aim of this CPG is to provide evidence-based recommendations in the management of ASD, particularly on the detection, assessment and intervention of the condition in children and adolescents.

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

Children and adolescents with ASD

TARGET GROUP/USER

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care of autism including:

i. Primary care providers (Family Medicine Specialists / Medical Officers / General Practitioners)
ii. Psychiatrists
iii. Paediatricians
iv. Psychologists
v. Audiologists
vi. Speech Language Therapists
vii. Occupational Therapists
viii. Social workers
xi. Nurses
xii. Pharmacists
xvii. Policy makers / programme managers

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The draft of these guidelines was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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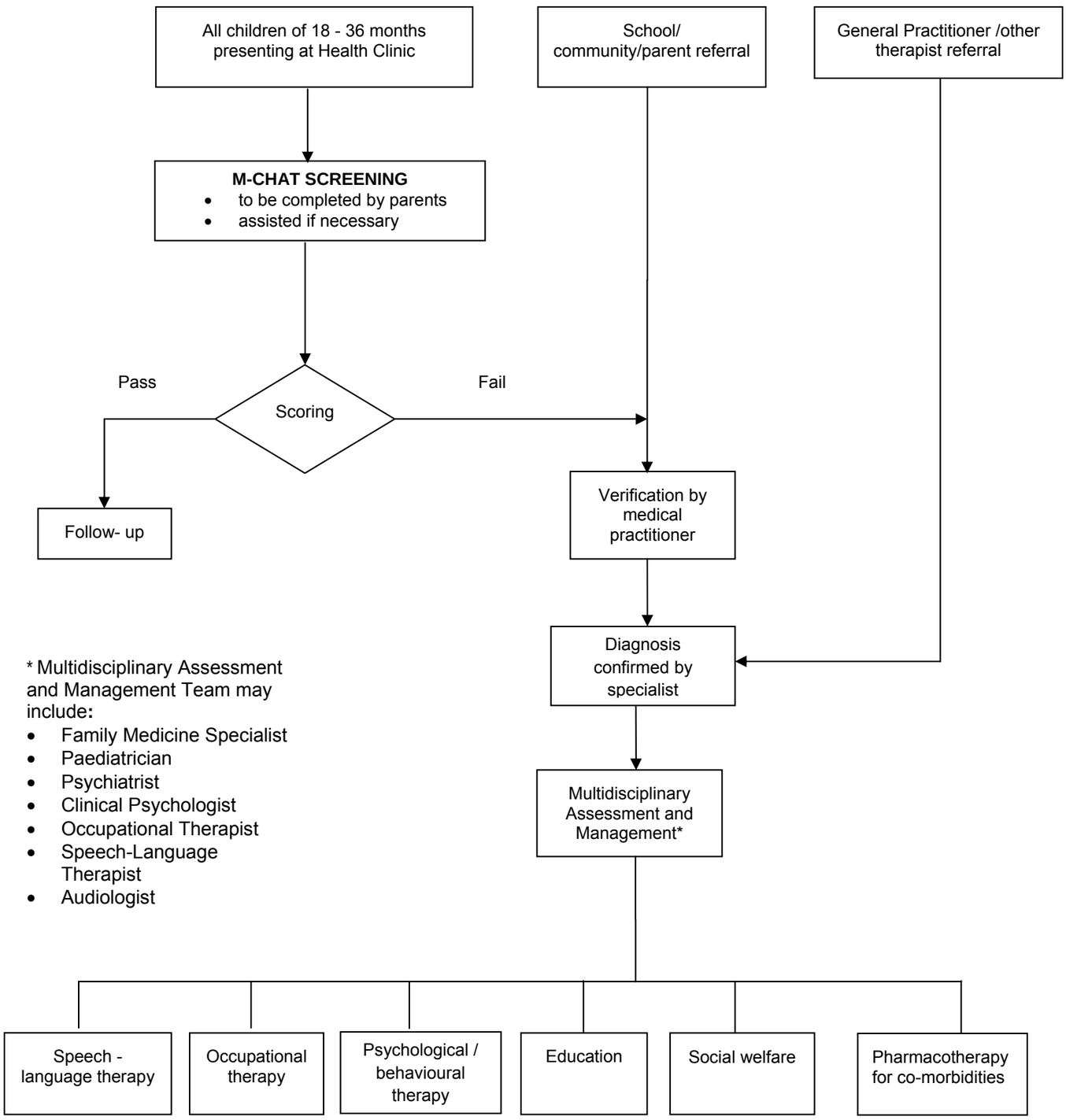
ALGORITHM ON MANAGEMENT OF CHILDREN WITH AUTISM SPECTRUM DISORDER



* Multidisciplinary Assessment and Management Team may include**:**

- Family Medicine Specialist
- Paediatrician
- Psychiatrist
- Clinical Psychologist
- Occupational Therapist
- Speech-Language Therapist
- Audiologist

Early intervention programme (EIP) is strongly advocated

1. INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterised by impairments in communication, behaviour and social functioning beginning in childhood. There is no local epidemiological study on ASD prevalence in Malaysia. However, a feasibility study on the use of MCHAT among children of 18 to 36 months of age in child health clinics by Ministry of Health Malaysia, the prevalence of ASD in Malaysia was approximately 1.6 in 1000.[1] In USA, the overall prevalence of ASD is 14.7 per 1,000 (one in 68) children aged 8 years and the prevalence shows an increasing trend over the years.[2]

Clinicians have been seeing an increasing number of children with speech delay and social communication difficulties who require further assessment. Many children with speech delay and behavioural issues are frequently placed in special education classes without an accurate diagnosis. The delay in diagnosis adds further stress to parents and caregivers who need assistance in the proper management of these children.

Early diagnosis and prompt intervention of children with ASD is crucial for the best outcome. The importance of recognising and initiating early referral to optimise the child's potential must be emphasised.

This has prompted the need to produce a CPG for the wide usage of healthcare providers in Malaysia as well as to provide assistance to parents of children with ASD. It is hoped that this CPG can give a clear picture to primary care providers to direct these children in an efficient manner. Referral pathways to specialists and various interventionists have been outlined in this CPG in order to facilitate this process.

2. RISK FACTORS

The aetiology of ASD is unclear. It is multi-factorial which includes both genetic vulnerability and environmental factors. Only risk factors deemed important by the DG and RC are discussed here.

- **Advancing Parental Age**

Parental age is among the most consistently studied risk factor and the risk for ASD increases with age.

- Maternal age:
  - >35 years old vs 25 - 29 years old (OR=1.31,95% CI 1.19 to 1.45)[3, level II-2]
  - >40 years old vs <30 years old (OR=2.1, 95% CI 1.48 to 2.86)[4, level II-2]
- Paternal age: Compared to ≤29 years old,[5, level II-2]
  - 49 years old (OR=1.42, 95%CI 1.07 to 1.87)
  - ≥50 years old (OR=2.21, 95% CI 1.26 to 3.88)
  - ≥55 years old (OR=4.36, 95% CI 2.09 to 9.09)
- First born of mother aged >35 years old and father aged >40 years old vs parents aged 25 - 29 years old, adjusted OR=3.1, 95%CI 2.0 to 4.7.[6, level II-2]

- **Prematurity** (<37 weeks gestation) in particular those born <33 weeks are at risk of developing ASD (OR=5.4, CI 1.1 to 27.7).[4, level II-2]

- **Encephalopathy** has OR for ASD ranging from 3.06 to 5.59[4, level II-2]

- **Vaccine**

Based on Cochrane systematic review of 10 studies, no significant association was found between MMR immunisation and autism.[7, level II-2] In another study, increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines during the first two years of life was not associated with risk of developing ASD.[8, level II-2]

- **Genetic Risk**

The adjusted relative recurrence risk of ASD is increased with increasing genetic relatedness:[3, level II-2]

- Monozygotic twins=153.0, 95% CI, 56.7 to 412.8

- Dizygotic twins=8.2, 95% CI, 3.7 to 18.1
- Full siblings=10.3, 95% CI, 9.4 to 11.3
- Maternal half siblings=3.3, 95% CI 2.6 to 4.2
- Paternal half siblings=2.9, 95% CI 2.2 to 3.7
- Cousins=2.0, 95% CI 1.8 to 2.2

The RR of ASD for infants with multiple older affected siblings is significantly 2.2 times higher than those who had only one older affected sibling.[9, level II-2]

- **Peri-conceptional supplement**

Use of folic acid supplement in mothers around the time of conception (four weeks before and eight weeks after pregnancy)[10, level II-2] or peri-conceptional prenatal vitamin intake (containing more iron, vitamin B6, vitamin B12 and folic acid 800µg as compared to ordinary multivitamins)[11, level II-2] appears to offer some benefit especially in those who are genetically susceptible.

Immunisation is not associated with the development of autism spectrum disorder.

RECOMMENDATION 1

- Screening for autism spectrum disorder should be emphasised in children with the following high risk factors:-
  - o Increased parental age
  - - Maternal age >40 years old
  - - Paternal age >50 years old
  - - First born of mother aged >35 years old and father aged >40 years old
  - o Prematurity of <33 weeks gestation
  - o Foetal encephalopathy
  - o Family history (**Grade C)**

3. SCREENING

Screening for ASD is important as early detection enables early intervention and better outcome. There are limited studies on the effectiveness of screening tools for ASD in children. Three systematic reviews (SRs) looked into the screening of young children for ASD and found that CHAT, MCHAT and Social Communication Questionnaire (SCQ) performed better in the screening. The primary studies were inadequate with small sample sizes, lack blinding between screening and diagnosis, and largely did not follow up children with negative results.[12, level II-1; 13, level II-1; 14, level II-1]

It is important to be aware that false positive or false negative results from any use of screening tests may delay correct diagnosis and cause unnecessary parental anxiety. The ultimate decision about the need for referral and further assessment should be made on clinical grounds.

a. Modified Checklist for Autism in Toddlers

Modified Checklist for Autism in Toddlers (MCHAT) is a 23-item questionnaire on child behaviour reported by parents for children aged between 18 and 24 months of age.[15, level III] It has been translated into Malay and Chinese languages for local use in healthcare facilities in Malaysia. Training is required for interpretation of the result.

The specificity of MCHAT was reported as 98% and follow-up of a subset of children at age 3.5 years resulted in a sensitivity of 100%.[14, level II-1] In a recent SR, the sensitivity, specificity and PPV were found to be 70% to 92%, 27% to 43% and 5.8% to 76% respectively. MCHAT was also better at detecting autism in children aged 24 months versus (vs) 18 months and those in high risk group in early intervention programme centres vs low risk group in the routine baby clinic.[12, level II-1]

b. Social Communication Questionnaire (formerly known as Autism Screening Questionnaire)

Social Communication Questionnaire (SCQ) is also a parent-rated questionnaire on children above four years old. It evaluates the social interaction, communication, language and stereotype behaviours of for possible autism or other ASD.[16, level III]

SCQ was better in detecting ASD in individuals over seven years of age (sensitivity of 86% to 90% and specificity of 78% to 86%) compared to children aged 2 - 3 years old (sensitivity 47% to 54% and specificity 89% to 92%).[13, level II-1]

c. Other Screening Tools

Other screening tools used are:

- Modified Checklist for Autism in Toddlers, Revised with Follow-up[17, level III]
- Checklist for Autism in Toddlers (CHAT)[12, level II-1; 14, level II-1; 18, level II-2]
- Gilliam Autism Rating Scale / Gilliam Autism Rating Scale Second Edition (GARS / GARS-2)
- Social Responsiveness Scale (SRS)
- Autism Spectrum Screening Questionnaire (ASSQ)
- Asperger Syndrome Diagnostic Scale (ASDS)
- Checklist for Autism in Toddlers for Chinese Children (CHAT-23)
- Child Behaviour Checklist (CBCL)

[13, level II-1, 19, level III, 20, level III]

RECOMMENDATION 2

- Modified Checklist for Autism in Toddlers may be used as a screening tool for autism spectrum disorder (ASD) among children of 18 - 24 months in primary care. **(Grade C)**
- Regardless of the screening result, children suspected of ASD by the family or other care provider should be referred for evaluation. **(Grade C)**

4. ASSESSMENT AND DIAGNOSIS

4.1 Initial Assessment – History, Developmental History and Physical Examination

Children with ASD may show early symptoms manifested by behavioural abnormalities. These include poor eye contact, impairment in visual tracking to an object, atypical response to name, less social smiling and delayed expressive and receptive language. The possibility of ASD should be considered if there are concerns about development delay or behaviour.[21]

Health care provider should take into consideration cultural and socioeconomic factors that may affect assessment.[22, level III]

4.1.1 Signs and symptoms of ASD[21] (refer to Appendix 3)

- Signs and symptoms in preschool children (less than 5 years old)
- Signs and symptoms in primary school children (5-11 years old)
- Signs and symptoms in secondary school children (more than 11 years old)

4.1.2 A complete history should include:

- Symptoms suspicious of ASD as in (refer to Appendix 3).
- Developmental history
- Behavioural problems and interaction with others
- Medical history including prenatal and perinatal history
- Psychiatric history – to assess co-existing mental disorders e.g. depression, anxiety.
- Family history
- Social history including schooling, home life, physical environment, social needs
- Medication history
- Parents'/carers' concerns

4.1.3 Physical examination should include:

- Presence of dysmorphic features
- Presence of congenital anomalies
- Stigmata of neurofibromatosis or tuberous sclerosis
- Speech/ communication skills and developmental assessment
- Hearing assessment
- Signs of physical abuse / self-harm

Other differential diagnoses to be considered during assessment are shown in Table 1:

Table 1: Differential diagnoses for autism[21]

- **Neurodevelopmental disorders:**
  - specific language delay or disorder
  - intellectual disability or global developmental delay
  - developmental coordination disorder (DCD)

- **Mental and behavioural disorders:**
  - attention deficit hyperactivity disorder (ADHD)
  - mood disorder
  - anxiety disorder
  - attachment disorders
  - oppositional defiant disorder (ODD)
  - conduct disorder
  - obsessive compulsive disorder (OCD)
  - psychosis

- **Conditions in which there is developmental regression:**
  - Rett's syndrome
  - epileptic encephalopathy

- **Other conditions:**
  - severe hearing impairment
  - severe visual impairment
  - maltreatment
  - selective mutism

4.2 Diagnosis

The diagnosis of ASD is made either by using criteria from the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV-TR, 2000 (**Appendix 4**) and DSM 5, 2013(**Appendix 5**)] OR 10th Revision of International Classification of Diseases [ICD-10] (**Appendix 6**).

The diagnosis of ASD requires disturbances in each of three domains: social relatedness, communication/play, and restricted interests and activities with onset by three years of age (DSM IV TR).

The ICD and DSM categorical system classifications have led to development of the Autism Diagnostic Interview-revised (ADI-R), the Diagnostic Interview for Social and Communication Disorders (DISCO) and the Developmental, Dimensional and Diagnostic Interview (3Di). Clinical experience and professional training is crucial to establish diagnosis. The observations in different setting e.g. school or home may be helpful.

ASD-diagnostic instruments that can be incorporated to facilitate assessment are ADOS, ADI-R, DISCO, 3Di, CARS. The Autism Diagnostic Observation Schedule (ADOS) is a reliable diagnostic instrument to supplement clinical history. Refer to **Appendix 7** for more details.

- **Autism Diagnostic Observation Schedule**

Autism Diagnostic Observation Schedule (ADOS) is a semi-structured assessment of communication, social interaction and play (or imaginative use of materials) for individuals suspected of having ASD. The ADOS consists of four modules, each of which is appropriate for children and adults of differing developmental and language levels, ranging from nonverbal to verbally-fluent.

- **Autism Diagnostic Interview-Revised**

The Autism Diagnostic Interview-Revised (ADI-R) is a structured interview conducted with the parents/carers of individuals for assessment of ASD. It is used for diagnostic purposes for anyone with a mental age of at least 18 months. The interview measures behaviour in the areas of reciprocal social interaction, communication and language, and patterns of behaviour.

- **Diagnostic Interview for Social and Communication Disorders**

Diagnostic Interview for Social and Communication Disorders **(**DISCO) is a detailed, semi-structured interview to be used with the parents/carers to identify the impairments of social interaction, social communication and social imagination together with the associated repetitive behaviours, and all the other features that can be found in ASD.

- **Childhood Autism Rating Scale**

Childhood Autism Rating Scale (CARS) is a 15-item behaviour observation rating scale to identify and differentiate children with autism from typical or other developmentally disabled individuals.

RECOMMENDATION 3
- Diagnosis of autism spectrum disorder should be made clinically based on comprehensive history and observation. Diagnostic tools may be used to assist in the clinical diagnosis. **(Grade C)**

4.3 Clinical Progression

Diagnosis of ASD based on clinical evaluation by trained and experienced clinician is relatively stable,[23, level II-3] Improvements in symptoms reported by parents do not translate to changes in diagnosis.[24, level II-3] The severity levels for ASD vary by context and fluctuate over time.

5. CO-MORBIDITIES AND OTHER DIFFICULTIES

Children with ASD can experience a wide spectrum of difficulties with emotion, attention, activity, thought, behavioural and medical problems. Diagnosis of co-morbid disorders is of major importance as it may cause significant clinical impairment in children with ASD. It is crucial that all comorbid conditions are appropriately assessed and managed.

a. Intellectual Disability

Extreme autistic traits are significantly associated with intellectual disability and poor academic performance ($p<0.001$). [25, level III] Among those with ASD, about half of them have intellectual disability.[26, level III]

b. Attention Deficit Hyperactivity Disorder[27, level III]

Prevalence of attention deficit hyperactivity disorder (ADHD) in children with ASD is 53% with the following subtypes:-

- 22% - hyperactive/impulsive
- 46% - inattentive
- 32% - combined

Compared to children with ASD alone, those with co-morbid ADHD:-

- are younger, with children between 5 and 7 years presenting more symptoms of hyperactivity ($p<0.05$)
- have a lower mean IQ ($p=0.01$)
- are on medication more often ($p<0.05$)
- do not show differences in gender ($p=0.59$) and type of ASD diagnosis ($p=0.11$)

c. Sleep Problems

Sleep problems in ASD occur in 44 - 83% of school aged children. Children with ASD significantly have:[28, level-III; 29, level II-2]

- at least one sleep problem
- sleep onset problems
- night waking

These findings are supported by polysomnography.[29, level II-2]

Cognitive or adaptive development did not predict severity of sleep problems in the ASD group.[28, level III]

d. Epilepsy

The prevalence of epilepsy in autism ranges from 7 - 46%. It is increased with greater intellectual disability, symptomatic autism, age, history of cognitive / developmental regression, usage of psychotropics and abnormality of electroencephalography (EEG).[30, level III; 31, level III]

The median age of onset for epilepsy is 14 years.[31, level III] Epileptiform abnormalities on EEG occur in 6 - 60% of autistic children.[30, level III]

The presence of epilepsy in children with ASD is significantly associated with psychiatric disorders.[32, level III]

e. Gastrointestinal Problems

Children with ASD are five times more common to have feeding problems than those without ASD (OR 5.11, 95% CI 3.74 to 6.97).[33, level II-2] Types of feeding problems are food selectivity (54%),[33, level II-2; 34, level II-2] food refusal (21%); behavioural rigidity during meals (17%) or their combinations (7%). Children with ASD tend to have a significantly lower consumption of calcium and protein compared to children without ASD, and a higher level of nutritional inadequacies.[33, level II-2]

Overall incidence of gastrointestinal symptoms in ASD does not differ from the general population, although there is an increased incidence of constipation in those with ASD.[35, level II-2]

f. Motor Coordination

Substantial motor coordination deficits occur in children with ASD across all age groups. Handwriting is very important for academic progress and social and communication development. Adolescents with ASD are known to have poor handwriting. The main predictors are intellectual ability (p=0.006) and motor skill (p=0.005).[36, level III]

g. Other Psychiatric Disorders[32, level III]

Prevalence of psychiatric disorders in children with ASD is as follows:

- 70.80% have at least one current psychiatric disorder (95% CI 58.2 to 83.4) although 57% had multiple diagnoses
- 62.80% (95% CI 49.8 to 75.9) have ADHD, emotional or behavioural disorder (oppositional defiant or conduct)
- 24.70% (95% CI 14.1 to 35.3) have Tourette syndrome, chronic tics, trichotillomania, enuresis, or encopresis (neuropsychiatric disorder)
- 41.90% (95% CI 26.8 to 57.0) have anxiety or phobic disorder
- 1.40% (95% CI 0 to 3.0) have depressive disorder
- 30% (95% CI 14.9 to 45.0) have oppositional or conduct disorder

There is no substantial evidence on the prevalence of psychosis in children with ASD.

6. INVESTIGATION

a. Audiological Evaluation

Most children with ASD present with speech and language delay. Therefore, audiological evaluation on them is an important component of initial assessment to rule out hearing impairment. Standard behavioural audiometric procedures are difficult to apply in children with ASD. Behavioural response in audiometric test is less reliable (≥15 dB) in younger children with the condition.[37, level III]

The electrophysiological tests use to evaluate hearing impairment are:

- Transient Evoked Otoacoustic Emissions (TEOAE)
- Auditory Brainstem Evoked-Response (ABR)
- Acoustic Reflexes (AR)

RECOMMENDATION 4

- Audiological assessment should be performed in children with autism spectrum disorder. **(Grade C)**

b. Other Investigations

ASD is predominantly a clinical diagnosis. Children with symptoms of ASD generally do not require intensive investigations. Investigations may be carried out in some children with ASD to establish underlying pathology, exclude treatable conditions and identify co-morbid conditions.

- **EEG**

There is insufficient evidence to support the use of EEG in the investigation of children with ASD without clinical seizures.[38, level II-2; 39, level II-2]

- **Genetic and Metabolic Investigations**

Genetic and metabolic studies are not routinely done in children with ASD. Genetic tests are done usually when there is a suspicion of syndromes for example Fragile X syndrome or when there is dysmorphism or macrocrania. These children have to be referred to a paediatrician or a geneticist for further evaluation.[40, level II-2] The association of inherited metabolic disorders and ASD is low.[41, level II-2]

- **Neuroimaging/Brain Imaging**

Brain Imaging studies are not routinely done in patients with ASD as a meta-analysis did not show any difference in the brains of children with ASD and controls.[42, level 1] Brain imaging is usually considered in selective cases where syndromes or neurological conditions are suspected and is usually done at tertiary levels.[43, level III]

- **Food Allergy**

There is no significant association between ASD and food allergies.[44, level II-2; 45, level II-2]

- **Mineral Analysis**

There is insufficient evidence to support the use of mineral analysis in ASD.

RECOMMENDATION 5

- Investigations should not be done routinely in children with autism spectrum disorder. **(Grade C)**

7. TREATMENT

Ideally, children with ASD should be managed by a multidisciplinary team as stated in the algorithm (page xiii). Early Intervention Programme (EIP) is advocated strongly especially for children below the age of three for better outcome. However, all children should be offered early intervention programmes upon diagnosis. Policy makers play important roles in the implementation of services for patients with ASD.

Children with autism spectrum disorder should be managed by a multidisciplinary team consisting:

- family medicine specialist
- paediatrician
- psychiatrist/child and adolescent psychiatrist
- clinical/educational psychologist/counsellor
- occupational therapist
- speech-language therapist
- social welfare officer
- educational officers
- teachers

7.1. Non-pharmacological Treatment

a. Applied Behaviour Analysis

Applied Behaviour Analysis **(**ABA) is the application of behavioural principles to everyday situations, that will over time increase or decrease targeted behaviours. This intervention is widely used in managing children with ASD and recognised as a safe and effective treatment. Although there are a number of ABA approaches, the Lovaas method is the most well-known and extensively researched.

The Lovaas method is used for children with ASD from the ages of two to eight and usually not later than 12. It consists of 35 - 40 hours per week of intensive interaction. The interaction is provided on a one-to-one basis for six to eight hours per day, five to seven days a week, for at least two years. Parental/family participation is an integral element of the interaction to ensure skills learnt in a classroom or clinic will be transferred into the home.

Lovaas therapy is superior to standard care or regular instruction. High-intensity Lovaas is superior to low-intensity Lovaas. In comparison to special education, Lovaas significantly improves the following:[46, level I]

- adaptive behaviour
- communication and interaction
- comprehensive language
- daily living skills
- expressive language
- overall intellectual functioning
- socialisation

There is inadequate evidence to pin-point specific behavioural intervention approaches to be most effective for individual children with ASD. Lovaas therapy and early intensive behavioural intervention variants, and the Early Start Denver Model result in some improvements in cognitive performance, language skills, and adaptive behaviour skills in some children.[47, level I]

RECOMMENDATION 6

- Applied Behaviour Analysis should be considered in the management of autism spectrum disorder. **(Grade A)**

b. Speech, Language and Communication Intervention

Children with ASD may have limited or no speech, poor joint attention and pragmatic skills, as well as difficulty to understand and interact with others. Those who receive speech and language therapy between two to three years old show improvement in expressive language at four years old (p<0.05).[48, level II-2]

It is important for family members to be active participants in a speech therapy session. Parents involvement in therapy of ASD children:-

- increase the number of communication acts and use of communication means (p<0.05)[49, level II-2]
- decrease autism behaviour and increase typical communication (p<0.05)[50, level I]

The various types of communication interventions for ASD children are discussed below.

- **Naturalistic Approach**

Responsive Education and Prelinguistic Milieu Teaching (RPMT) facilitates intentional communication during the prelinguistic period in children with developmental delay. Whereas Reciprocal Imitation Training (RIT) is an imitation intervention developed for young children with autism.

RPMT significantly improves social communication and language learning in ASD children compared to Picture Exchange Communication System (PECS) in terms of:-

- object exchange turns and requesting[51, level I]
- initiating joint attention[51, level I]
- increase in object interest[52, level I]

RIT improves elicited and spontaneous imitation of objects and gestures in young children with autism (<5 years old) with a greater play repertoire compared to controls (p<0.05).[53,level I]

- **Augmentative and Alternative Communication**

Augmentative and Alternative Communication (AAC) describes other communication methods that can help ASD children with limited speech or no speech to communicate. It is divided into aided and unaided. Unaided AAC consists of nonverbal means of natural communication including gestures and facial expressions. Aided AAC requires some additional external support such as a communication board with visual-graphic symbols using pictures, line drawings or printed words.

AAC improves communication skills (IRD=0.99, 84% CI 0.98 to 0.99), social skills (IRD=0.90, 84% CI 0.84 to 0.95), spelling (IRD=0.79, 84% CI 0.76 to 0.82) and challenging behaviour (IRD=0.80, 84% CI 0.76 to 0.84) in individuals with ASD.[54, level III]

Picture Exchange Communication System (PECS) is a six-phased aided AAC. It is designed to facilitate functional and spontaneous communication skills. Its use in ASD children helps them to develop speech.

PECS improves communication skills in individuals with ASD in terms of:-
- non-imitative spoken communication acts (p=0.03)[55, level I]
- number of different non-imitative words (p=0.04)[55, level I]
- functional communication (IRD=0.65, 84% CI 0.59 to 0.73)[56, level III]
- challenging behaviour (IRD=0.45, 84% CI 0.48 to 0.73)[56, level III]
- socialisation (IRD=0.73, 84% CI 0.53 to 0.93)[56, level III]

PECS increases requesting skills in individuals with autism based on Percentage of Non-overlapping Data (PND) score.[57, level I] It also increases frequency and number of non-imitative spoken communication compared to RPMT in pre-schoolers with ASD (p<0.05).[51, level I] PECS has larger effects than other picture-based AAC systems in targeted behaviours which include communication and social skills (IRD=0.99, 84% CI 0.98 to 0.99).[56, level III]

PECS training is effective for pre-school children (p<0.001), single ASD diagnosis (p=0.005) and those completed all six phases (p=0.005).[56, level III]

A speech generating device (SGD) is an electronic device that produces speech for the user. It is an aided AAC and often used with graphic symbols. SGD with enhanced milieu teaching and signing increase requesting skills in individual with autism based on PND score.[57, level I] SGD has larger effects than other picture-based AAC systems in targeted behaviours which include communication and social skills, although it is not statistically significant.[56, level III]

There is no retrievable evidence on unaided AAC.

- **Video Modelling**

Video modelling is a mode of teaching that uses video recording to provide visual model of the targeted skill to ASD children. Types of video modelling include video modelling, video self-modelling and “video modelling with other as model”.

Video modelling and video self-modelling moderately improve social communication skills, functional skills and behavioural functioning in ASD children.[58, level III] “Video modelling with other as model” improves play skills, independent living and social-communicative skills in ASD children (p<0.05).[59, level III]

Children with ASD at two to three years of age who receive speech and language therapy show improvement in expressive language at four years of age.

RECOMMENDATION 7
- Children with autism spectrum disorder should receive speech, language and communication intervention as needed. **(Grade A)**

c. Social Story

Social story helps children with ASD to understand the nuances of interpersonal communication for effective and appropriate interaction. It can be performed by occupational therapist, speech-language therapist, psychologist, teacher or caregiver who is trained. Social story improves total social skills and social isolation (p<0.005),[60, level I] and appropriate social behaviours (mean

PND=56) in ASD children. It also reduces inappropriate behaviours (mean PND=87).[61, level III] Standard and directive social story interventions are equally effective in eliciting, generalising and maintaining the targeted social skills in children with autism (p<0.001).[62, level I]

d. Occupational Therapy

ASD may affect the individual's self-care ability, play, academic performance and social activities at home, school and community. Sensory processing dysfunction or sensory integration dysfunction are also affected in 50 - 90% of children with ASD.[63; 64; 65; 66] Motor skill development is also impaired compared to their typically developing peers.[67;68;69]

Occupational therapy provides assessment and intervention to maximise activities of daily living. There is a significant correlation between sensory-motor performance and self-care (r=0.53, p=0.001)[70] The interventions provided by occupational therapists include sensory integration therapy, self-help skills, sensory-motor skills, social skills, perception motor, and behavioural and developmental intervention.[71]

- **Social Skills and Self-help Skills**

Social skills and self-help skills intervention improve deficits in the skills in ASD.[72, level III] For social skill intervention, the effectiveness was supported by a Cochrane SR which showed improvement in overall social competence (ES=0.47, 95% CI 0.16 to 0.78) and friendship quality (ES=0.41, 95% CI 0.02 to 0.81) in ASD.[73, level I]

- **Sensory Integration Therapy**

Sensory Integration Therapy (SIT) is often used by occupational therapists to treat children with ASD.[74] The treatment typically involves providing sensory input using appropriate modalities.

SIT significantly improves sensory processing, motor skills and social functioning compared to fine motor intervention as rated by parents and teachers. It also significantly decreases autistic mannerisms.[75, level I]

Behavioural and developmental interventions for ASD significantly reduce stereotypic behaviours, off task behaviours and touch aversion.[46, level I]

- **Joint Attention Intervention**

Joint Attention(JA) refers to the child's capacity to coordinate attention with a social partner around an object or event.[76] JA intervention in ASD improves joint attention in teacher-child play (p=0.036) and joint engagement in mother-child play (p=0.015).[77, level I]

- **Perceptual Motor Training**

Perception motor training is skills related with movement such as hand eye coordination. In a quasi-experimental study, perceptual motor training increased the attention of children with ASD (p<0.05).[78, level II-1]

- **Home-Based Developmental, Individual-Difference, Relationship-Based/Floortime**

In Individual-Difference, Relationship-Based **(**DIR) Floortime therapy, adults help children to develop their circles of communication by playing with them at their developmental level and building on their strengths. Home-based DIR/Floortime™ intervention at an average of 14.2 hours/week for a year significantly improves developmental skills and reduces autistic symptoms in 47% ASD children.[79, level I]

- **Music Therapy**

In a RCT, children with autism were randomised to receive music therapy and play at different sequence. Generally, music therapy improved joint attention behaviours in both groups (p=0.01). However, joint attention skills improved significantly when play was conducted before music therapy while eye contact events occurred significantly longer when music therapy was instituted before play.[80, level I]

RECOMMENDATION 8

- Occupational therapy should be offered to the children with autism spectrum disorder. **(Grade A)**

d. Parent Education and Support

Managing children with ASD is a huge challenge to their families. Children need certain degree of parental involvement and supports in acquiring social and communication skills. Parents without proper training may contribute to the failure of children applying the skills outside the classrooms. Thus, parental involvement is important to ensure the continuity of intervention.

Parental training improves communication skills (p=0.01) and IQ level of children with autism (MD=16.82, 95% CI 0.58 to 33.06). It is also beneficial in providing parents with knowledge of autism (MD=2.70, 95% CI 4.70 to 0.70), enabling them to manage their stress effectively (MD=1.52, 95% CI 0.40 to 2.64).[81, level I]

Children's functional verbal utterances increase following parental training ($p<0.05$) and are maintained at follow-up (2 - 4 months). The relationship between parent fidelity to the training and child communication improves from pre-training to follow-up ($p< 0.05$).[82, level III]

RECOMMENDATION 9

- Parental training should be offered to parents of children with autism spectrum disorder. **(Grade A)**

e. Cognitive Behaviour Therapy

Cognitive Behaviour Therapy (CBT) is used in children with ASD who have anxiety and mood disorders.

The application of modified CBT is effective in reducing anxiety in children with Asperger subtype but not in other subtypes of ASD.[83, level I] CBT modalities that are effective in the treatment of anxiety in ASD include Coping Cat,[84, level I; 85, level II-3] Building Confidence CBT Program[86, level I; 87, level I] and modules specifically developed for ASD children.[88, level I] However, most of the primary studies were done on children with high verbal intelligence.

RECOMMENDATION 10

- Cognitive behaviour therapy may be offered to autism spectrum disorder children with high verbal intelligence having anxiety disorder. **(Grade A)**

f. Treatment and Education of Autistic and Related Communication Handicapped Children

Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) is a structured teaching system based on a close collaboration between parents and professionals. It can be used for individuals of all ages and skill levels with ASD.

There is no significant difference between TEACCH and standard care in imitation skills and eye-hand integration,[46, level I] although there is moderate to large effect sizes (ES) in social functioning (ES=0.65, 95% CI 0.15 to 1.15) and maladaptive behaviour (pooled ES= -0.92, 95% CI -1.51 to -0.33) [89, level I]

Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) may be useful in the management of children with autism spectrum disorder.

g. Diet

Gluten and casein-free diet and dimethylglycine are not effective in the management of autism.[90, level I; 91, level I]

Omega-3 supplements have no significant effect on social interaction, communication, stereotypy or hyperactivity.[92, level I]

Dietary-related intervention has no significant benefit in children with autism spectrum disorder.

7.2. PHARMACOTHERAPY

In ASD, medications are used in the treatment of co-morbid disorders.

a. Atypical Antipsychotics (AAP)

The use of atypical antipsychotics in ASD is preferred due to the reduced propensity to cause extrapyramidal symptoms.

- **Risperidone**

Risperidone in low doses (up to 2 mg/day in children weighing from 20 - 45 kg and up to 3.5 mg/ day in those weighing over 45 kg) may be beneficial in some features of ASD.[93, level I] A meta-analysis of three RCTs in children with ASD suggested that short-term use of risperidone significantly improved:-

irritability	(MD= -8.09, 95% CI -12.99 to -3.19)
social withdrawal/lethargy	(MD= -1.00, 95% CI -5.03 to -0.97)
hyperactivity	(MD= -8.98, 95% CI -12.01 to -5.94)
stereotypy	(MD= -1.71, 95% CI -2.97 to -0.45)
inappropriate speech	(MD= -1.93, 95% CI -3.79 to -0.07)

However, there was a higher risk of weight gain (MD=1.78, 95% CI 1.15 to 2.41) in the treatment group compared to placebo.[94, level I]

- **Aripiprazole**

A meta-analysis of two RCTs in children with ASD suggested that aripiprazole up to 15mg per day may be efficacious in treating:-

irritability	(MD=-6.17, 95% CI -9.07 to -3.26)
hyperactivity	(MD=-7.93, 95% CI -10.98 to -4.88)
stereotypy	(MD=-2.66, 95% CI -3.55 to -1.77)
inappropriate speech	(MD=-1.43, 95% CI -2.60 to -0.27)

Adverse effects such as weight gain (MD=1.13, 95% CI 0.71 to 1.54), sedation (MD=4.28, 95% CI 1.58 to 11.60), drooling (MD=9.64, 95% CI 1.29 to 72.10) and tremor (MD=10.26, 95% CI 1.37 to 76.63) may occur more often in the treatment compared to the placebo.[95, level I]

- **Other AAPs**

  - **Quetiapine**

    Low dose quetiapine (≤150 mg/d) is efficacious in reducing aggression (p=0.028) and improving sleep quality (p=0.014) in ASD at eight weeks. No significant difference in body weight is observed and the adverse effects are mild.[96, level II-3]

  - **Olanzapine**

    Olanzapine up to 20 mg per day improves CGI-I score in Pervasive Developmental Disorder (PDD) at eight weeks (p=0.012). However, clinically significant weight gain is more likely to occur in individuals treated with the medication (p=0.028).[97, level I]

  - **Paliperidone**

    Paliperidone up to 12 mg per day is efficacious for significant irritability in individuals with autism (p=0.0002). The safety profile is acceptable except for raised prolactin level in males (p=0.0001).[98, level II-3]

  - **Ziprasidone**

    Ziprasidone up to 160 mg/day is efficacious in reducing irritability (*p*=0.05) and hyperactivity (*p*=0.01) in autism at six weeks. The serious side effect of QTc prolongation

of ziprasidone may offset the arguably minimal benefits associated with its use. (p=0.04).[99, level II-3]

Conventional antipsychotics such as haloperidol are used less frequently due to its high incidence of severe adverse reactions.

b. Antidepressants

- **Selective Serotonin Reuptake Inhibitors (SSRI)**

A Cochrane SR looked into the efficacy of various Selective Serotonin Reuptake Inhibitors (SSRIs) in the treatment of children with ASD. There was no evidence of effect of SSRIs in children on core symptoms and severity of the disorder. There was also reports on emerging evidence of harm such as seizure, poor appetite and weight loss.[100, level I]

- **Tricyclic Antidepressants**

A Cochrane SR concluded that there was limited and conflicting evidence of effect and the side effect of Tricyclic Antidepressants (TCA) as a treatment option in ASD. For example, a study done in 1993 favoured clomipramine against placebo but later study in 2001 showed non-significant findings with substantial side effects. Further research is required before TCAs can be recommended for treatment of individuals with ASD.[101, level I]

c. Others

- **Methylphenidate**

Methylphenidate was found to be more efficacious than placebo among PDD subjects in crossover RCT followed by open-label continuation of three months duration. Parent-rated and teacher-rated ABC hyperactivity subscale scores during crossover phase were significantly lower in different methylphenidate dosages and the response maintained in the continuation phase. Reported side effects were loss of appetite, sleep difficulties and irritability.[102, level I]

- **Atomoxetine**

Atomoxetine can decrease ADHD symptoms in children with ASD at ten weeks. The most common adverse effects are gastrointestinal problems, irritability, reduced appetite and weight loss.[103, level I]

- **Valproate**

In a RCT, divalproate sodium significantly reduced irritability compared to placebo. The findings were robust even after controlling intelligence quotient (IQ) differences.[97, level I] It was well tolerated. Most side effects were mild to moderate in severity and resolved with small changes in dosing and did not require a discontinuation of medication.

Except for Risperidone and Aripiprazole, the drugs listed above are for off label use.

- **Melatonin**

Melatonin is an endogenous neurohormone produced predominantly in the pineal gland. It is commonly used for insomnia in children and has a favourable side-effect profile.[104]

In a meta-analysis, melatonin was more efficacious than placebo in the treatment of ASD in terms of:[105, level I]

- Increased Sleep duration by 44 minutes (Hedge's g=1.07, 95% CI 0.49 to 1.65)
- Shorter Sleep onset latency by 39 minutes (Hedge's g=2.46, 95% CI 1.96 to 2.98)

The findings above were supported by a recent RCT whereby a combination of CBT and melatonin was statistically most efficacious in reducing insomnia symptoms compared to either modality or placebo when used alone.[106, level I]

In terms of safety, mild side effects reported in the meta-analysis were headache, diarrhoea and dizziness.[105, level I]

RECOMMENDATION 11

- Children with autism spectrum disorder may be offered:
  - atypical antipsychotics as short-term treatment for irritability. **(Grade A)**
  - methylphenidate and atomoxetine for hyperactivity. **(Grade A)**
  - melatonin for sleep difficulties. **(Grade A)**

7.3 Traditional and Complementary Medicine

Any other treatment modality not described above is grouped under traditional and complementary medicine. The following treatment modalities have poor evidence or show no effectiveness to support their use in children with ASD:-

- chelation[107, level II-3]
- secretin[108, level I]
- fatty acids[92, level I]
- vitamin B6-magnesium[109, level I]
- vitamin B12[110, level I]
- acupuncture[111, level I]
- hyperbaric oxygen therapy[103, level I]

There is no retrievable evidence for vitamin A, vitamin C, Trimethylglycine, cupping, ayurvedic medicine or homeopathy in the treatment of ASD.

8. SOCIAL WELFARE SERVICE

Children with ASD should be referred to the Department of Social Welfare at their respective districts. This will enable the child to be registered for benefits such as:

- placement to special needs education if warranted
- welfare support including financial allowances from the department
- free education and health services in the public sector
- others

The registration form should be completed by the medical practitioner/medical officer at the point of diagnosis.

9. MONITORING AND PREPARATION OF TRANSITION FROM ADOLESCENTS TO ADULT SERVICES

Children with ASD require monitoring clinically for physical growth, behaviour and development, as well as co-morbidities, associated medical problems, sexuality and safety. The main goal is for children with ASD to become independent and successful in all aspects of their life, leading to a higher quality of life while they exit the school system. However, there is a lack of reliable and valid measures to evaluate progress and change of a child's behaviour and functioning over time after the diagnosis of ASD.[112, level II-2]

Transition for children with ASD should be discussed and planned early by all involved in their management. ASD children have varying intellectual and functional abilities, hence the transition into adulthood has to be planned early according to their individual abilities.[113, level III] Vocational training, post-secondary education, day care activities and supervised employment are options for these.[114, level II-1]

Care for children and adolescents with ASD should be continued in adult health services. There is a need for establishment of this service to support children and adolescents when they enter adulthood**.**

10. IMPLEMENTATION OF GUIDELINES

Implementation of this CPG is the responsibility of each healthcare provider. Mechanism should be in place to review care provided against the guidelines recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guidelines in individual hospital and clinic.

a. Facilitating and Limiting Factors

The facilitating factors in implementing these CPG are:-

- **Dissemination of CPG**
  - Availability and dissemination of CPG to health care providers (hard and soft copies)
  - Annual conferences and updates on child development

- **Implementation of CPG**
  - Screening
  - MCHAT use optimised in existing child health record book
  - Staff training on MCHAT
  - Public awareness via world autism day
  - Assessment, diagnosis and intervention
  - Accessibility to relevant multidisciplinary team
  - Active involvement of government and non-governmental organisations

The limiting factors in the implementation are:

- Limited awareness and knowledge of detection and subsequent referral
- Variation of practice and treatment at different levels of care
- Limited financial and human resource
- Lack of training at all levels of healthcare providers
- Lack of networking with private practitioners

b. Potential Resource Implications

- Widespread distribution of CPG to healthcare personnel via printed copies
- Reinforce training of healthcare providers via regular seminars and workshops
- Establish ASD registry in Malaysia
- Develop a multidisciplinary team in secondary and tertiary care levels.

To enhance the utilisation of these CPG on Management of Autism Spectrum Disorder in children and adolescents, the following clinical audit indicators for quality management are proposed:-

$$\text{Percentage of children aged 18 - 24 months screened with MCHAT} = \frac{\text{Number of children aged 18 - 24 months screened with MCHAT within a year}}{\text{Number of children aged 18 - 24 months attended child health clinic in same duration}} \times 100\%$$

$$\text{Percentage of children with failed MCHAT referred for further assessment*} = \frac{\text{Number of children with failed MCHAT referred for further assessment within a year}}{\text{Number of children failed MCHAT in same duration}} \times 100\%$$

*Assessment by MDT

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

The following MeSH terms or free text terms were used either singly or in combination, search was limit to English, human, 2001 to current and children 0-18 years old

TCM

1. Autistic Disorder/
2. (Autistic adj1 disorder*).tw.
3. Autism*.tw.
4. 1 or 2 or 3
5. Vitamin B 12/
6. (b12 adj1 vitamin).tw.
7. cyanocobalamin.tw.
8. cobalamin.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. Vitamin B 6/
12. Vitamin B6.tw.
13. Vitamin B 6.tw.
14. Pyridoxine.tw.
15. Pyridoxamine.tw.
16. Picolines.tw.
17. /or 11-16
18. Vitamin A/
19. vitamin a.tw.
20. vitamin a1.tw.
21. all trans retinol.tw.
22. Retinol.tw.
23. 11-cis-retinol.tw.
24. /or 18 -23
25. Fish Oils/
26. (fish adj1 oil*).tw.
27. liver oils fish.tw.
28. fish liver oils.tw.
29. oils fish liver.tw.
30. /or 25-29
31. Zinc/
32. Zinc.tw.
33. 31 or 32
34. Melatonin/
35. Melatonin.tw.
36. 34 or 35
37. 4 and 17
38. 4 and 24
39. 4 and 30
40. 4 and 33
41. 4 and 36
42. trimethylglycine.mp.
43. Trimethylglycine.tw.
44. Magnesium/
45. Magnesium.tw.
46. 42 or 43 or 44 or 45
47. 4 and 46
48. Hyperbaric Oxygenation/
49. therapies hyperbaric oxygen.tw.
50. hyperbaric oxygenation*.tw.
51. hyperbaric oxygen therap*.tw.
52. oxygen therapies hyperbaric.tw.
53. oxygenation hyperbaric.tw.
54 therap* hyperbaric oxygen.tw.
55. oxygen therap* hyperbaric.tw.
56. HBOT.tw.
57. /or 48 - 56
58. 4 and 57
59.Ascorbic Acid/
60. (acid adj1 ascorbic).tw.
61. (sodium adj1 ascorbate).tw.
62. magnorbin.tw.
63. (ferrous adj1 ascorbate).tw.
64. acid l-ascorbic.tw.
65. magnesium ascorbicum.tw.
66. l-ascorbic acid.tw.
67. vitamin c.tw.
68. l ascorbic acid.tw.
69. ascorbic acid monosodium salt.tw.
70. hybrin.tw.
71. ascorbic acid monosodium salt.tw.
72. hybrin.tw.
73. /or59 -72
74. 4 and 73
75.Chelation Therapy/
76.(Chelation adj 1 therap*).tw
77. 75 or 76
78. 4 and 77

Speech Language Therapy

1. Autistic Disorder/
2. autism*.tw.
3. (Autistic adj1 disorder*).tw.
4. 1 or 2 or 3
5. Speech Therapy/
6. Language Therapy/
7. Speech language therap*.tw.
8. (Speech adj1 therap*).tw.
9. (Language adj1 therap*).tw.
10. (Language adj1 train*).tw.
11. 5 or 6 or 7 or 8 or 9 or 10
12. 4 and 11
13. Augmentative communication*.tw.
14. Alternative communication*.tw.
15. Augmentative alternative communication.tw.
16. AAC.tw.
17./or 13-16
18. 4 and 17
19.Communication Aids for Disabled/
20. Augmentative communication*.tw.
21. Alternative communication*.tw.
22. Augmentative alternative communication.tw.
23. AAC.tw.
24. AAC intervention*.tw.
25./or 19-24
26. 4 and 25
27.Picture Exchange Communication System*.tw.
28. PECS.tw.
29. 27 or 28
30. 4 and 29
31.naturalistic behavio?r*.tw.
32. natural language teach*.tw.
33. 31 or 32
34. 4 and 33
35. milieu therap*.tw.
36. milieu teach*.tw.
37. 35 or 36
38. 4 and 37
39. incidental teach*.tw.
40. 4 and 39
41.facilitate teach*.tw.
42. facilitate communication*.tw.
43. facilitated communication*.tw.
44. 41 or 42 or 43
45. 4 and 44
46.discrete trial train*.tw.
47. discrete trial teach*.tw.
48. discrete trial instruct*.tw.
49. discrete trial intervention*.tw.
50. 46 or 47 or 48 or 49
51. 4 and 50
51.Video instruct*.tw.
52. Video model*.tw.
53. Video self-model*.tw.
54. Point-of-view video*.tw.
55. /or 51- 54
56. 4 and 55

Behaviour intervention

1. Autism*.tw.
2. (Autistic adj1 disorder*).tw.
3. (Conditioning adj1 therap*).tw.
4. Behavio?r intervention*.tw.
5. (Behavio?r adj1 modification*).tw.
6. (Therap* adj1 behavio?r*).tw.
7. Behavior Therapy/
8. Autistic Disorder/
9. Applied behavior analysis.tw.
10. 1 or 2 or 8
11. 3 or 4 or 5 or 6 or 7 or 9
12. 10 and 11

Occupational therapy

1. Autistic Disorder/
2. Autism*.tw.
3. (autistic adj1 disorder*).tw.
4. 1 or 2 or 3
5. Sensory processing*.tw.
6. 4 and 5
7.Fine motor.mp.
8. Occupational Therapy/
9. (occupational adj1 therap*).tw.
10. 7 or 8 or 9
11. 4 and 10
12.Toilet training*.tw.
13.(toilet * adj1 training*).tw.
14. 12 or 13
15. 4 and 14

Diet intervention

1. Autistic Disorder/
2. Autism*.tw.
3. (Autistic adj1 disorder*).tw.
4. Diet*.tw.
5. 1 or 2 or 3
6. 4 and 5

Appendix 2

CLINICAL QUESTION

1. RISK FACTORS

- What are the risk factors for ASD?

2. CO-MORBIDITIES

- What are the common co-morbidities of ASD?

3. SCREENING

- What are the effective screening tools for diagnosis or to detect ASD?

4. ASSESSMENT AND DIAGNOSIS

- What is the Initial assessment – history, developmental history, physical examination?
- Is direct observational assessment (DOS) accurate in diagnosing ASD?
- Are DISCO, CARS and ADI-R useful for diagnosing ASD?

5. INVESTIGATION

- What are the effective hearing test can be used in ASD to detect deafness/ hearing loss?
- Is lead analysis a useful investigation tool in autistic children?
- Do autistic children need to be assessed for food allergies?
- Do autistic children need routine EEG to be done?
- What is the role of neuroimaging, metabolic and genetic testing in the diagnosis of ASD?

6. TREATMENT

- Is speech language therapy effective in treating children with ASD?
- What is/are speech, language & communication intervention/s effective for children with ASD?
- Is social story effective in treating children with ASD?
- Is behaviour intervention effective in treating ASD?
- Is occupational therapy intervention effective for children with ASD?
- Is parental education intervention effective in treating children with ASD?
- Is cognitive behaviour intervention effective in treating children with ASD?
- Is TEACCH (treatment and education of autistic and related communication handicapped children) an effective and safe intervention for children with autism?
- Is diet Intervention effective in autism?
- Is pharmacological therapy (antipsychotic, SSRI, TCA, Methyphenidate, Divalproex sodium) effective and safe for children with ASD?
- Is chelation, secretin, fatty acids, melatonin, Vitamin B12, HBOT, Vitamin B6-Mg therapy safe and efficacious treatment for ASD?

8. MONITORING AND PREPARATION OF TRANSITION FROM ADOLESCENCE TO ADULT MEDICAL SERVICES?

- What services are available for children with ASD in the transition into adulthood?

Appendix 3

Signs and symptoms of possible autism in preschool children (or equivalent mental age) [NICE, 2011]

Social interaction and reciprocal communication behaviours
Spoken language Language delay (in babble or words, for example less than ten words by the age of 2 years) Regression in or loss of use of speech Spoken language (if present) may include unusual: • non-speech like vocalisations • odd or flat intonation • frequent repetition of set words and phrases ('echolalia') • reference to self by name* or 'you' or 'she/he' beyond 3 years Reduced and/or infrequent use of language for communication, for example use of single words although able to speak in sentences *Part of the spoken language section may not be applicable to local setting
Responding to others Absent or delayed response to name being called, despite normal hearing Reduced or absent responsive social smiling Reduced or absent responsiveness to other people's facial expressions or feelings Unusually negative response to the requests of others (demand avoidant behaviour) Rejection of cuddles initiated by parent or carer, although may initiate cuddles themselves
Interacting with others Reduced or absent awareness of personal space, or unusually intolerant of people entering their personal space Reduced or absent social interest in others, including children of his/her own age – may reject others; if interested in others, may approach others inappropriately, seeming to be aggressive or disruptive Reduced or absent imitation of others' actions Reduced or absent initiation of social play with others, plays alone Reduced or absent enjoyment of situations that most children like, for example, birthday parties Reduced or absent sharing of enjoyment
Eye contact, pointing and other gestures Reduced or absent use of gestures and facial expressions to communicate (although may place adult's hand on objects) Reduced and poorly integrated gestures, facial expressions, body orientation, eye contact (looking at people's eyes when speaking) and speech used in social communication Reduced or absent social use of eye contact assuming adequate vision Reduced or absent joint attention shown by lack of: • gaze switching • following a point (looking where the other person points to – may look at hand) • using pointing at or showing objects to share interest
Ideas and imagination Reduced or absent imagination and variety of pretend play
Unusual or restricted interests and/or rigid and repetitive behaviours Repetitive 'stereotypical' movements such as hand flapping, body rocking while standing, spinning, finger-flicking Repetitive or stereotyped play, for example opening and closing doors Over-focused or unusual interests Excessive insistence on following own agenda Extremes of emotional reactivity to change or new situations, insistence on things being 'the same' Over or under reaction to sensory stimuli, for example textures, sounds, smells Excessive reaction to taste, smell, texture or appearance of food or extreme food fads

Signs and symptoms of possible autism in primary school children (aged 5 –11 years or equivalent mental age) NICE, 2011

Social interaction and reciprocal communication behaviours
Spoken language Spoken language may be unusual in several ways: • very limited use • monotonous tone • repetitive speech, frequent use of stereotyped (learnt) phrases, content dominated by excessive • information on topics of own interest • talking 'at' others rather than sharing a two-way conversation • responses to others can seem rude or inappropriate
Responding to others Absent or delayed response to name being called, despite normal hearing Reduced or absent responsive social smiling Reduced or absent responsiveness to other people's facial expressions or feelings Unusually negative response to the requests of others (demand avoidant behaviour) Rejection of cuddles initiated by parent or carer, although may initiate cuddles themselves
Responding to others Reduced or absent response to other people's facial expression or feelings Reduced or delayed response to name being called, despite normal hearing Subtle difficulties in understanding other's intentions; may take things literally and misunderstand sarcasm or metaphor Unusually negative response to the requests of others (demand avoidant behaviour)
Interacting with others Reduced or absent awareness of personal space, or unusually intolerant of people entering their personal space Reduced or absent social interest in people, including children of his/her own age – may reject others; if interested in others, may approach others inappropriately, seeming to be aggressive or disruptive Reduced or absent greeting and farewell behaviours Reduced or absent awareness of socially expected behaviour Reduced or absent ability to share in the social play or ideas of others, plays alone Unable to adapt style of communication to social situations, for example may be overly formal or inappropriately familiar Reduced or absent enjoyment of situations that most children like
Eye contact, pointing and other gestures Reduced and poorly integrated gestures, facial expressions and body orientation, eye contact (looking at people's eyes when speaking), and speech used in social communication Reduced or absent social use of eye contact assuming adequate vision Reduced or absent joint attention shown by lack of: • gaze switching • following a point (looking where the other person points to – may look at hand) • using pointing at or showing objects to share interest
Ideas and imagination Reduced or absent flexible imaginative play or creativity, although scenes seen on visual media (for example, television) may be re-enacted Makes comments without awareness of social niceties or hierarchies
Unusual or restricted interests and/or rigid and repetitive behaviours Repetitive 'stereotypical' movements such as hand flapping, body rocking while standing, spinning, finger-flicking Play repetitive and oriented towards objects rather than people Over-focused or unusual interests Rigid expectation that other children should adhere to rules of play Excessive insistence on following own agenda Extremes of emotional reactivity that are excessive for the circumstances Strong preferences for familiar routines and things being 'just right' Dislike of change, which often leads to anxiety or other forms of distress (including aggression) Over or under reaction to sensory stimuli, for example textures, sounds, smells Excessive reaction to taste, smell, texture or appearance of food or extreme food fads
Other factors that may support a concern about autism Unusual profile of skills or deficits (for example, social or motor coordination skills poorly developed, while particular areas of knowledge, reading or vocabulary skills are advanced for chronological or mental age) Social and emotional development more immature than other areas of development, excessive trusting (naivety), lack of common sense, less independent than peers

Signs and symptoms of possible autism in secondary school children (older than 11 years or equivalent (mental age) [NICE, 2011]

Social interaction and reciprocal communication behaviours
Spoken language Spoken language may be unusual in several ways: • very limited use • monotonous tone • repetitive speech, frequent use of stereotyped (learnt) phrases, content dominated by excessive • information on topics of own interest • talking 'at' others rather than sharing a two-way conversation • responses to others can seem rude or inappropriate
Interacting with others Reduced or absent awareness of personal space, or unusually intolerant of people entering their personal space Long-standing difficulties in reciprocal social communication and interaction: few close friends or reciprocal relationships Reduced or absent understanding of friendship; often an unsuccessful desire to have friends (although may find it easier with adults or younger children), social isolation and apparent preference for aloneness Reduced or absent greeting and farewell behaviours Lack of awareness and understanding of socially expected behaviour Problems losing at games, turn-taking and understanding 'changing the rules' May appear unaware or uninterested in what other young people his or her age are interested in Unable to adapt style of communication to social situations, for example may be overly formal or inappropriately familiar Subtle difficulties in understanding other's intentions; may take things literally and misunderstand sarcasmor metaphor Makes comments without awareness of social niceties or hierarchies Unusually negative response to the requests of others (demand avoidant behaviour)
Eye contact, pointing and other gestures Poorly integrated gestures, facial expressions, body orientation, eye contact (looking at people's eyes when speaking) assuming adequate vision, and spoken language used in social communication
Ideas and imagination History of a lack of flexible social imaginative play and creativity, although scenes seen on visual media(for example, television) may be re-enacted
Unusual or restricted interests and/or rigid and repetitive behaviours Repetitive 'stereotypical' movements such as hand flapping, body rocking while standing, spinning, finger-flicking Preference for highly specific interests or hobbies A strong adherence to rules or fairness that leads to argument Highly repetitive behaviours or rituals that negatively affect the young person's daily activities Excessive emotional distress at what seems trivial to others, for example change in routine Dislike of change, which often leads to anxiety or other forms of distress including aggression Over or under reaction to sensory stimuli, for example textures, sounds, smells Excessive reaction to taste, smell, texture or appearance of food and/or extreme food fads
Other factors that may support a concern about autism Unusual profile of skills and deficits (for example, social or motor coordination skills poorly developed, while particular areas of knowledge, reading or vocabulary skills are advanced for chronological or mentalage) Social and emotional development more immature than other areas of development, excessive trusting (naivety), lack of common sense, less independent than peers

Appendix 4

DSM IV-TR DIAGNOSTIC CRITERIA FOR AUTISTIC DISORDER (DSM-IV – TR)

The essential features of Autistic Disorder are the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interests. Manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual. Autistic Disorder is sometimes referred to as *early infantile autism, childhood autism,* or *Kanners autism*.

A. A total of six (or more) items from 1, 2, and 3, with at least two from 1, and one each from 2 and 3:

1. Qualitative impairment in social interaction, as manifested by at least two of the following:
   a. Marked impairment in the use of multiple nonverbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
   b. Failure to develop peer relationships appropriate to developmental level
   c. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (for example, by a lack of showing, bringing, or pointing out objects of interest)
   d. Lack of social or emotional reciprocity

2. Qualitative impairments in communication as manifested by at least one of the following:
   a. Delay in or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gestures or mime)
   b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
   c. stereotyped and repetitive use of language or idiosyncratic language
   d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

3. Restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following:
   a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
   b. apparently inflexible adherence to specific, nonfunctional routines or rituals
   c. stereotyped and repetitive motor mannerisms (for example, hand or finger flapping or twisting, or complex whole-body movements)
   d. persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

(Adapted from the Diagnostic and Statistical Manual of Mental Disorder, fourth Edition: DSM-IV-TR. Washington D.C.: American Psychiatric Association; 2000)

Appendix 5

DIAGNOSTIC CRITERIA FOR AUTISM SPECTRUM DISORDER (DSM-5)

Autism Spectrum Disorder 299.00 (F84.0)

Diagnostic Criteria

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures: to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behaviour (refer to table below).

B. Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circum scribed or perseverative interests).
4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse re sponse to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behaviour (refer to table below).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if;

With or without accompanying intellectual impairment
With or without accompanying language impairment
Associated with a known medical or genetic condition or environmental factor (Coding note: Use additional code to identify the associated medical or genetic condition.)
Associated with another neurodevelopmental, mental, or behavioural disorder (Coding note: Use additional code[s] to identify the associated neuro-developmental, mental, or behavioural disorder[s].)
With catatonia (refer to the criteria for catatonia associated with another mental disorder, pp. 119-120, for definition) (Coding note: Use additional code 293.89 [F06.1] catatonia associated with autism spectrum disorder to indicate the presence of the co morbid catatonia).

Severity levels for autism spectrum disorder

Severity level	Social communication	Restricted, repetitive behaviours
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and how has markedly odd nonverbal communication.	Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful response to social overtures of others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful.	Inflexibility of behaviour causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

(Adapted from the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition: DSM-5. Washington D.C.: American Psychiatric Association; 2014)

Appendix 6

INTERNATIONAL CLASSIFICATION OF DISEASES (ICD) 10

F84 PERVASIVE DEVELOPMENTAL DISORDERS

F84.0 Childhood autism

A. Presence of abnormal or impaired development before the age of three years, in at least one out of the following areas:
(1) receptive or expressive language as used in social communication;
(2) the development of selective social attachments or of reciprocal social interaction;
(3) functional or symbolic play.

B. Qualitative abnormalities in reciprocal social interaction, manifest in at least one of the following areas:
(1) failure adequately to use eye-to-eye gaze, facial expression, body posture and gesture to regulate social interaction;
(2) failure to develop (in a manner appropriate to mental age, and despite ample opportunities) peer relationships that involve a mutual sharing of interests, activities and emotions;
(3) A lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people's emotions; or lack of modulation of behaviour according to social context, or a weak integration of social, emotional and communicative behaviours.

C. Qualitative abnormalities in communication, manifest in at least two of the following areas:
(1) a delay in, or total lack of development of spoken language that is not accompanied by an attempt to compensate through the use of gesture or mime as alternative modes of communication (often preceded by a lack of communicative babbling);
(2) relative failure to initiate or sustain conversational interchange (at whatever level of language skills are present) in which there is reciprocal to and from responsiveness to the communications of the other person;
(3) stereotyped and repetitive use of language oridiosyncratic use of words or phrases;
(4) abnormalities in pitch, stress, rate, rhythm and intonation of speech;

D. Restricted, repetitive, and stereotyped patterns of behaviour, interests and activities, manifest in at least two of the following areas:
(1) an encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus; or one or more interests that are abnormal in their intensity and circumscribed nature although not abnormal in their content or focus.
(2) apparently compulsive adherence to specific, non-functional, routines or rituals;
(3) stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting, or complex whole body movements;
(4) preoccupations with part-objects or non-functional elements of play materials (such as their odour, the feel of their surface, or the noise or vibration that they generate);
(5) distress over changes in small, non-functional, details of the environment.

E. The clinical picture is not attributable to the other varieties of pervasive developmental disorder; specific developmental disorder of receptive language (F80.2) with secondary socio-emotional problems; reactive attachment disorder (F94.1) or disinhibited attachment disorder (F94.2); mental retardation (F70-F72) with some associated emotional or behavioural disorder; schizophrenia (F20) of unusually early onset; and Rett's syndrome (F84.2).

F84.1 Atypical autism

A. Presence of abnormal or impaired development at or after age three years (criteria as for autism except for age of manifestation).

B. Qualitative abnormalities in reciprocal social interaction or in communication, or restricted, repetitive and stereotyped patterns of behaviour, interests and activities (criteria as for autism except that it is not necessary to meet the criteria in terms of number of areas of abnormality).

C. The disorder does not meet the diagnostic criteria for autism (F84.0).

Autism may be atypical in either age of onset (F84.11) or phenomenology (84.12), these two types being differentiated with a fifth character for research purposes. Syndromes that are atypical in both respects should be coded F84.12.

F84.5 Asperger's syndrome

A. A lack of any clinically significant general delay in spoken or receptive language or cognitive development.
Diagnosis requires that single words should have developed by two years of age or earlier and that communicative phrases be used by three years of age or earlier. Self-help skills, adaptive behaviour and curiosity about the environment during the first three years should be at a level consistent with normal intellectual development. However, motor milestones may be somewhat delayed and motor clumsiness is usual (although not a necessary diagnostic feature). Isolated special skills, often related to abnormal preoccupations, are common, but are not required for diagnosis.

B. Qualitative abnormalities in reciprocal social interaction (criteria as for autism).

C. An unusually intense circumscribed interest or restricted, repetitive, and stereotyped patterns of behaviour, interests and activities (criteria as for autism; however it would be less usual for these to include either motor mannerisms or preoccupations with part- objects or non-functional elements of play materials).

D. The disorder is not attributable to the other varieties of pervasive developmental disorder; schizotypal disorder (F21); simple schizophrenia (F20.6); reactive and disinhibited attachment disorder of childhood (F94.1 and .2); obsessional personality disorder (F60.5); obsessive-compulsive disorder (F42**).**

(Adapted from the ICD-10 Classification of Mental and Behavioural Disorders:Diagnostic criteria for Research. Geneva: World Health Organization; 1993)

Appendix 7

DIAGNOSTIC TOOLS

Diagnostic Tool	Description	Sensitivity	Specificity	Comments
Autism Diagnostic Interview-Revised (ADI-R)[115], level III	• Structured interview conducted with the parents/carers of individuals for assessment of ASD. • It is used for diagnostic purposes for anyone with a mental age of at least 18 months. • The interview measures behaviour in the areas of reciprocal social interaction, communication and language, and patterns of behaviour	1.0	>0.97	• The levels of agreement between the ADI-R and ADOS is moderate in social (κ=0.56) and communication (κ=0.48) algorithm cut-offs scores. • The level of agreement between the ADI-R and ADOS is substantial in diagnosing autism (κ=0.62) and moderate for spectrum diagnosis (κ=0.54).
Diagnostic Interview for Social and Communication Disorders (DISCO)[116], level II-3	• Semi-structured interview used by the parents/carers to identify the impairments of social interaction, social communication and social imagination together with the associated repetitive behaviours	0.80	0.79	• DISCO accurately identify ASD in young children with an average intelligence or mild intellectual disability • The agreement between DISCO algorithm and ADOS was substantial (k=0.69, p<0.001).
Childhood Autism Rating Scale (CARS)[117], level II-2	• Consists of 14 domains assessing behaviours associated with autism, with the 15th domain rating general impressions of autism. • Each domain is scored on a scale ranging from one to four; higher scores are associated with a higher level of impairment. • Scores below 30 indicate that the individual is in non-autistic range.	2 years old: 0.79 4 years old: 0.86	2 years old: 0.81 4 years old: 0.80	• In younger children, CARS is useful to distinguish ASD from Pervasive developmental disorder not otherwise specified (PDD-NOS). • Using an ASD cut-off score of 25.5, CARS produced the highest level of agreement among diagnostic instruments and clinical judgement: • **2 years old**: • CARS and DSM IV, κ=0.75, p<0.001 • CARS and ADOS, κ=0.70, p<0.001 • **4 years old**: • CARS and DSM IV, κ=0.74, p<0.001 • CARS and ADOS, κ=0.73, p <0.001
Autism Diagnostic Observation Schedule (ADOS)[118],	• Semi-structured assessment of communication, social interaction and play (or	0.82	0.60	• The prevalence of best-estimate clinical diagnosis at nine years is 43% for ADOS alone, 82% when combined with clinical judgement and 90% when combined with

Diagnostic Tool	Description	Sensitivity	Specificity	Comments
level III, 119, level II-2	imaginative use of materials) for individuals suspected of having ASD. • Consists of four modules, each of which is appropriate for children and adults of differing developmental and language levels, ranging from nonverbal to verbally-fluent.			both clinical judgement and ADI-R.

LIST OF ABBREVIATIONS

3Di	the Developmental, Dimensional and Diagnostic Interview
ABA	Applied Behaviour Analysis
AAC	Augmentative and Alternative Communication
ABC	Aberrant Behavior Checklist
ABR	Auditory Brainstem Evoked Response
ADHD	Attention Deficit Hyperactive Disorder
ADI-R	Autism Diagnostic Interview- revised
ADOS	The Autism Diagnostic Observation Schedule
AGREE	Appraisal of Guidelines for Research and Evaluation
AR	Acoustic Reflexes
ASD	Autism Spectrum Disorder
ASSQ	Autism Spectrum Screening Questionnaire
ASDS	Asperger Syndrome Diagnostic Scale
AUC	Area Under the Curve
CARS	Childhood Autism Rating Scale
CBCL	Child Behaviour Checklist
CCTs	Clinical Control Trials
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence Interval
CGI	Clinical Global Impression
CHAT	Checklist for Autism in Toddlers
CHAT-23	Checklist for Autism in Toddlers for Chinese Children
CPG	Clinical Practice Guidelines
CAM	Complementary and alternative medicine
Db	Decibel
DCD	Developmental Coordination Disorder
DIR	Individual-Difference, Relationship-Based
DISCO	the Diagnostic Interview for Social and Communication Disorders
DG	Development Group
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorders-IV TR
DSM 5	Diagnostic and Statistical Manual of Mental Disorders 5
EEG	Electroencephalography
ES	Effect size
GARS	Gilliam Autism Rating Scale
GARS-2	Gilliam Autism Rating Scale Second Edition
G-I-N	Guidelines International Network
IVF	In Vitro Fertilisation
IgM	Immunoglobulin M
ICD-10	International Classification of Diseases
IQ	Intelligence quotient
IRD	Improvement Rate Difference
JA	Joint attention
MaHTAS	Malaysia Health Technology Assessment Section
M-CHAT	Modified Checklist for Autism in Toddlers
MD	Mean different
MDT	Multi Disciplinary Team
MMR	Measles, Mumps, Rubella
MOH	Ministry of Health
OCD	obsessive compulsive disorder
ODD	oppositional defiant disorder
OT	Occupational Therapy
OR	Odd Ratio
PANESS	Physical and Neurological Examination for Soft Signs
P	P Value
PDD	Pervasive developmental disorder
PDD-NOS	Pervasive developmental disorder not otherwise specified
PECS	Picture Exchange Communication System
PND	Percentage of Non-overlapping Data
PPV	positive predictive value
RC	Review Committee
RCT	Randomised control trial
RIT	Reciprocal Imitation Training

RPMT	Responsive Education and Prelinguistic Milieu Teaching
RR	Risk Ratio
SCI	Social Communication Intervention
SCQ	Social Communication Questionnaire
SMD	Standard Mean Difference
SIT	Sensory Integration Therapy
SR	Systematic Reviews
SRS	Social Responsiveness Scale
SSRI	Selective Serotonin Reuptake Inhibitors
SGD	Speech Generating Device
TEOAE	Transient Evoked Otoacoustic Emissions
TEACCH	Treatment and Education of Autistic and Related Communication Handicapped Children
TCA	Tricyclic Antidepressants
WMD	Weighted Mean Differences

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